International Seminar on Therapeutic Applications of Radiopharmaceuticals

Hyderabad, India
18-22 January 1999

PROGRAMME

BOOK OF EXTENDED SYNOPSES

29-52

IAEA-SR-209
SECRETARIAT:

A.K. Padhy ......................................................... Scientific Secretaries
H. Vera Ruiz....................................................... Conference Services
H. Schmid ......................................................... Local Organizer
S.K. Chirala ....................................................... Local Organizer

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Working language: English

Resolutions: No resolutions may be submitted for consideration on any subject and no votes will be taken.
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PROGRAMME

18 January 1999 a.m.

08.00 - 09.00 REGISTRATION
09.00 - 10.00 INAUGURATION

10.00 - 11.00 Invited lecture I
Chairpersons : Subbarao K. (INDIA)
SR-209/L7 "Current trends in radionuclide therapy"
Britton K.E. (UK)

11.00 - 11.30 Coffee break

11.30 - 12.30 Scientific session I: Radiopharmaceuticals I
Chairpersons : Gangadharan S. (INDIA), Vera Ruiz H. (IAEA)

SR-209/1 Preparation of Y-90 and some preliminary results on labelling the radiopharmaceuticals
Malja S., Schomacker K., Damani G., Cuci T., Sallaku A., Malja E. ALBANIA
SR-209/19 Y-90 of high purity for clinical applications
Xiques Castillo A., Isaac Olvé K., Olivé Alvarez E. CUBA
SR-209/21 Y-90 and Rh-105 labelled preparations - potential therapeutic agents
Venkatesh M., Usha .C., Pillai M.R.A. INDIA
SR-209/24 Radiobioconjugate therapy : Silver and gold as candidate radionuclides - concepts and achievements

12.30 - 14.00 Lunch
18 January 1999 p.m.

14.00 - 14.30 **Invited lecture II**
Chairpersons: Chinol D.M. (ITALY), Hazra D.K. (INDIA)

SR-209/19
“The role of mathematical models in the optimization of radiopharmaceutical therapy”
Divgi C. (USA)

14.30 - 15.30 **Scientific session II: Radiopharmaceuticals II**
Chairpersons: Chinol D.M. (ITALY), Hazra D.K. (INDIA)

SR-209/25
Production and radiochemical processing of therapeutic radionuclides
*M.R.A. Pillai, P.R. Unni, K. Kothari, A.R. Mathakar* INDIA

SR-209/38
Study on the preparation and stability of Re-188-biomolecules via EHDP
*Ferro-Flores G., Garcia-Salinas L., Paredes-Gutierrez L., Hashimoto K., Melendez-Alafort L., Murphy C.A.* MEXICO

SR-209/43
Re-186-Bleomycine: Radiopharmaceutical for diagnosis and therapy
*Szostak S., Tustanowski S., Birkenfeld B., Almakiewicz R.* POLAND

SR-209/49
Rhenium-186 direct labeled IgG
*Lungu V.V., Mihaiescu G., Dumitrescu G.* ROMANIA

15.30 - 16.00 Coffee break

16.00 - 17.30 **Scientific session III: General I**
Chairpersons: McEwan A.J.B. (CANADA), Pillai M.R.A. (INDIA)

SR-209/34
Therapeutic application of Holmium-166 Chitosan complex in the treatment of hepatocellular carcinoma
*Jong-Tae Lee, Jong-Doo Lee, Kyong-Bae Park* KOREA, Rep. of

SR-209/29
Liver cancer as a model for radioimmunotargeting

SR-209/28
Experimental animal models for radioimmunotargeting

SR-209/4
Therapeutic trials to control metastatic cancer with Y-90 DOTA Lanreotide
*Riccabona G., Moncayo R., Virgolini I.* AUSTRIA

SR-209/3
Pirocarbotrat™: A new radiopharmaceutical labeled with P-32 for the treatment of solid tumors. Therapeutic action and radiodosimetric calculations
*Zubillaga M., Boccio J., Calmonovici G., Caro R., Nicolini J., Ughetti R., Sapia S., Frahm I., Gamboni M.* ARGENTINA
19 January 1999 a.m.

09.00 - 09.30 **Invited lecture III**
Chairpersons: Riccabona G. (AUSTRIA), Krishna B.A. (INDIA)

SR-209/L3
"Management of thyroid cancer with I-131: An overview"
Samuel A.M. (INDIA)

09.30 - 10.30 **Scientific session IV: Thyroid cancer I**
Chairpersons: Riccabona G. (AUSTRIA), Krishna B.A. (INDIA)

SR-209/6
Radioiodine therapy in management of thyroid carcinoma - A review of 138 patients
Afroz S., Hossain S., Hafiz N., Taslima D.A., Rashid H. BANGLADESH

SR-209/39
Treatment of thyroid cancer with I-131 at INMOL, Lahore
Asghar S.A., Sajjad R., Ilyas N. PAKISTAN

SR-209/46
Radiation dose rates from patients receiving Iodine-131 therapy for carcinoma of the thyroid
in 1997 and 1998 at I.P.O.F.G. in Lisbon
Nogueira A.R., Rêzio M.T., Ferreira T.C. PORTUGAL

SR-209/23
What should be the Optimal Dose of $^{131}$I for Remnant Ablation in Differentiated Thyroid Cancer?
Bal C.S., Padhy A.K., Basu A.K. INDIA

10.30 - 11.00 Coffee break

11.00 - 12.30 **Scientific session V: Thyroid cancer II**
Chairpersons: Padhy AK. (IAEA), Poshyachinda M. (THAILAND)

SR-209/8
Radioiodine therapy for pediatric patients with thyroid cancer
Demiditchik Y.E., Kirinuk S. BELARUS

SR-209/9
A complex evaluation of the efficiency of I-131 ablation in patients with differentiated
thyroid carcinoma after surgery
Milanov S.H., Mladenov B.I. BULGARIA

SR-209/41
Effectivity of Iodine-131 for ablating metastatic lesions in differentiated thyroid carcinoma
Obaldo J.M., Cruz F.B. PHILIPPINES

SR-209/40
Comparison of Tc-99m Tetrofosmin and I-131 whole body scintigraphy for follow-up of well
differentiated thyroid carcinoma after I-131 therapy
Obaldo J.M., Cruz F.B., Blanch R.G.F. PHILIPPINES

SR-209/48
Differentiated thyroid carcinoma: Retrospective analysis of 50 patients with 5 years
follow-up

SR-209/55
Ablation rate in 410 patients with differentiated thyroid cancer
Aras G., Kacik N.O., Yagmur C., Demir H., Gençoglu A.E., Köylüoğlu I.,

SR-209/60
Results of treatment with I-131 in the group of 1054 patients with differentiated carcinoma of
thyroid
Tasic S. YUGOSLAVIA

12.30 - 14.00 Lunch
19 January 1999 p.m.

14.00 - 14.30 Invited lecture IV
Chairpersons : Samuel A.M. (INDIA), Olea E. (CHILE)

SR-209/L6 “The management of hyperthyroidism”
Poshyachinda M. (THAILAND)

14.30 - 15.30 Scientific session VI: Hyperthyroidism
Chairpersons : Samuel A.M. (INDIA), Olea E. (CHILE)

SR-209/11 Thyroid function status after 131-radioiodine therapy for hyperthyroidism using ablative and non ablative doses
Rivera M., Pineda P., Massardo T., Michelsen H., Lillo R., Araya V., Liberman C., Sierralta P. CHILE

SR-209/42 Radioiodine therapy in hyperthyroidism
Barrenechea E.A. PHILIPPINES

SR-209/59 Evaluation on results of 20 years treating hyperthyroidism by I-131
Phan Sy An, Mai Trong Khoa, Tran Dinh Ha VIETNAM

SR-209/12 I-131 therapy for thyroid disease. Dose, new regulations and patient advices.
Amaral H., Michaud P. CHILE

SR-209/61 Standardisation of different protocol of I-131 treatment in patients of graves disease and role of lithium
Rakesh Kumar, Pandey AK, Pant GS, Padhy AK, Gupta AK, Amini AC. INDIA

15.30 - 16.00 Coffee break

16.00 - 16.30 Invited lecture V
Chairpersons : Britton K.E. (UK), Pan Z. (CHINA)

SR-209/L4 “Radiolabelled peptides: New radiopharmaceuticals for targeted therapy”
Chinol D.M. (ITALY)

16.30 - 17.30 Scientific session VII: General II
Chairpersons : Britton K.E. (UK), Pan Z. (CHINA)

SR-209/14 Preparation, quality control and animal test of Sm-153-DTPA-Octreotide
Fan Hongliang, Jin Xiaohai, Bai Hongsheng, Wang Fan, Chen Daming CHINA

SR-209/20 Studies in rats on Octreotide labelled with Ga-67 - A potential radiopharmaceutical agent for the treatment of somatostatin receptor-positive tumors
Lázničková A., Lázniček M., Trejtnar F., Macke H.R. CZECH REPUBLIC

SR-209/17 Preparation and quality control of I-131 mIBG
Huang Yong, Kong Xiangrong, Liu Yishu, Qing Weiming, Tian Jianchun CHINA

SR-209/36 Meta (I-131) Iodobenzylguanidine (MIBG) : An analogue of the adrenergic neuron blocking guanethidine
Abudata A.J., Alkatali S.E., Abdunabi M.H. LIBYA

SR-209/37 The development of meta-iodobenzylguanidine analogues for the therapy of neuroendocrine and other tumors
Vaidyanathan G., Zalutsky M.R. USA
20 January 1999 a.m.

09.00 - 09.30 **Invited lecture VI**

Chairpersons: Lele R.D. (INDIA), Divgi C. (USA)

SR-209/L8

"Experience of radionuclide therapy with monoclonal antibodies and peptide"

Britton K.E. (UK)

09.30 - 10.00 **Invited lecture VII**

Chairpersons: Lele R.D. (INDIA), Divgi C. (USA)

SR-209/L3

"Monoclonal antibodies to the pretargeting approach: Developments in radiopharmaceuticals for RIT"

Chinol D.M. (ITALY)

10.00 - 10.30 **Scientific session VIII: Monoclonal Antibodies**

Chairpersons: Lele R.D. (INDIA), Divgi C. (USA)

SR-209/15

The preventive study of gastric cancer peritoneal micrometastasis in nude mice with Re-188-labeled monoclonal antibody 3H11

Yang Zhi, Zhang Meiyong, Lin Baohui, Zhao Changying, Han Yan, Mou Aping, Ma Yunxia

CHINA

SR-209/37

Labeling of MoAb with Sm-153-HETA

Ferro-Flores G., Ramirez F. De M., Pedraza-Lopez M., Tendilla J.I., Melendez-Alafort L., Murphy C.L.

MEXICO

10.30 - 11.00 Coffee break

11.00 - 12.30 **Scientific session IX: Radiopharmaceuticals III**

Chairpersons: Narasimhan D.V.S. (IAEA), Knapp F.F. Jr. (USA)

SR-209/16

The binding assay of Sm-153-EDTMP in vivo and in vitro

Chen Daming, Jin Xiaohai, Wang Yuqing, Bai Hongsheng, Fan Hongquang, Zhang Jingming

CHINA

SR-209/31

Sm-153 complexes of phosphonate ligands


INDIA

SR-209/45

Influence of central metal ion on bone deposition of EDTMP chelates with different radionuclides

Pawik D., Wozniak I., Mikolajczak R., Garnuszek P., Licinska P.

POLAND

SR-209/5

Trials of optimized dosimetry for Sm-153-EDTMP-Therapy to improve therapeutic effects

Riccabona G., Moncayo-Naveda R., Oberladstatter O.

AUSTRIA

SR-209/7

Radiopharmaceuticals of DTPA, DMSA and EDTA labelled with Holmium-166

Rahman M., Matsuoka H., Takami S., Torunuma K.

BANGLADESH

SR-209/32

Studies on the preparation and evaluation of colloidal chomic phosphate-P-32 for possible therapeutic use

Prabhakar G., Mehra K.S., Ramamoorthy N.

INDIA

SR-209/35

MAG2GABA-Biocytin synthesized with new intermediates for radiolabeling Tc-99m and Re-188

Soon Hyuk Ahn, Tae Hyun Choi, Sang Moo Lim, Chang Woon Choi, Seung Dae Yang, Kwang Sun Woo, Wee Sup Chung

KOREA, Rep. of

12.30 - 14.00 Lunch
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09.00 - 09.30 Invited lecture VIII
Chairpersons: Nair G. (INDIA), Amaral H. (CHILE)
SR-209/L1 "Dosimetry in Radionuclide therapy"
Riccabona G. (AUSTRIA)

09.30 - 10.30 Scientific session X: Treatment of Bone Pain I
Chairpersons: Nair G. (INDIA), Amaral H. (CHILE)
SR-209/10 Bone pain palliation with P-32 therapy
Chakarova A., Petkova E., Sergieva S., Hristova N. BULGARIA
SR-209/50 Phosphorus-32 for bone pain palliation due to bony metastases, its safety and efficacy in patients with advanced cancer
Fettich J., Nair G., Padhy A.K., Stare J., Nair N., Moralles R., Tanumihardja M., Riccabona G. SLOVENIA
SR-209/47 Therapy with Strontium-89 for bone pain palliation in prostate cancer patients
Vieira M.R., Sequeira J., Salgado L. PORTUGAL

10.30 - 11.00 Coffee break

11.00 - 11.30 Invited lecture IX
Chairpersons: Kumaresan K. (INDIA), Fettich J. (SLOVENIA)
SR-209/L2 "New aspects of radionuclide therapy of bone and joint diseases"
Fischer M. (GERMANY)

11.30 - 12.30 Scientific session XI: Radiation Synovectomy
Chairpersons: Kumaresan K. (INDIA), Fettich J. (SLOVENIA)
SR-209/22 Ho-166-Hydroxy apatite particles for radiation synovectomy
Unni P.R., Pillai M.R.A. INDIA
Pusuwan P., Asavatanabodee P., Chaudakshetrin P., Virawat N., Songkhla N. THAILAND
SR-209/33 Radiation synovectomy in chronic knee synovitis: Self experience and review of the literature
Garty I., Mader R. ISRAEL

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14.00 - 14.30 Invited lecture X
Chairpersons: Padhy A.K. (INDIA), Vera Ruiz H. (IAEA)
SR-209/L11 "Rhenium radioisotopes for therapeutic radiopharmaceutical development"
Knapp F.F. Jr. (USA)

14.30 - 15.30 Scientific session XII: Treatment of Bone Pain II
Chairpersons: Padhy A.K. (INDIA), Vera Ruiz H. (IAEA)

SR-209/56 Rhenium-188-HEDP in the treatment of pain in bone metastases
  Gaudiano P.J., Savlo E., Robles A., Muniz S., Leon A., Verdera S., Martinez G.,
  Hermida J.C., Knapp K.K. Jr. URUGUAY

SR-209/54 Palliative effect of Re-186-HEDP in different cancer patients with bone metastases
  Kucuk N.O., Ibis E., Aras G., Baltaci S., Ozalp G., Beduk Y., Canakci N., Soylu A.
  TURKEY

SR-209/27 Radiochemical studies and pharmacological behaviour of $^{186}$Re complexes of phosphonate ligands
  Kothari K.K., Banerjee S., Samuel G., Unni P.R., Sarma H.D., Pillai M.R.A. INDIA

15.30 - 16.00 Coffee break

16.00 - 17.30 Scientific session XIII: Treatment of Bone Pain III
Chairpersons: Fischer M. (GERMANY), Barrenechea E.A. (PHILIPPINES)

SR-209/2 Sm-153-EDTMP for palliation of pain from osseous metastases: Preparation and biodistribution studies
  Saichi B., Larbi R., Saada B., Benzaid A., Aliane M., Bouyoucef S.E., Madoui A.
  ALGERIA

SR-209/30 Radiochemical and biological studies, including in non-human primates, towards indigenous development of Sm-153-EDTMP
  Saraswathy P., Mehro K.S., Ranganatha D.K., Balasubramanian P.S., Das M.K.,
  Ananthakrishnan M., Ramamoorthy N., Gunasekaran S., Shanthy N., Narasimhan S.,
  Pomnalar J.R. INDIA

SR-209/13 Efficacy and toxicity of 153-Samarium-EDTMP locally produced in the treatment of painful skeletal metastases
  Oleg E., Quintana J.C., Nagel J., Arenas L., Tomicic M., Gil M.C., Araya G. CHILE

SR-209/18 Random comparison study of the clinical response to Sm-153 EDTMP 1.0 mCi/Kg and 1.5 mCi/kg
  Pan Z., Zhu S. CHINA
22 January 1999 a.m.

09.00 - 09.30 **Invited lecture XI**
Chairpersons: Knapp F.F. Jr. (USA), Samuel A.M. (INDIA)
SR-209/L10 “Radioimmunotherapy: Opportunities, obstacles and challenges, with special reference to developing countries”
Divgi C. (USA)

09.30 - 10.30 **Scientific session XIV : General III**
Chairpersons: Knapp F.F. Jr. (USA), Samuel A.M. (INDIA)

SR-209/44 Preparation and evaluation of various P-32 sources for intravascular brachytherapy

SR-209/26 Use of TLD in dosimetry of beta emitters for therapy

SR-209/58 Astatinated radiopharmaceuticals for targeted alpha particle therapy
*Vaidyanathan G., Zalutsky M.R.* USA

SR-209/53 Microdosimetry of Astatine-211 and comparison with that of Iodine-125
*Ünak T.* TURKEY

SR-209/51 Dosimetric aspect on radioimmunotherapy using the alpha-particle emitter Astatine-211
*Palm S., Jacobsson L.* SWEDEN

10.30 - 11.00 Coffee break

11.00 - 12.30 **Panel discussion**
Chairpersons: Britton K.E. (UK), Lele R.D. (INDIA)

“Future trend in radionuclide therapy”

12.30 - 13.00 **Closing**

13.00 - 14.00 Lunch
II. BOOK OF EXTENDED SYNOPSES

The material in this book has been supplied by the authors and has not been edited. The views expressed remain the responsibility of the named authors and do not necessarily reflect those of the government of the designating Member State(s). The IAEA cannot be held responsible for any material reproduced in this book.
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Preparation and quality control of $^{131}$I MIBG

Meta (I-131) iodobenzylguanidine (MIBG): An analogue of the adrenergic neuron blocking guanethidine

The development of meta-iodobenzylguanidine analogues for the therapy of neuroendocrine and other tumors

Wednesday 20 January 1999

Experience of radionuclide therapy with monoclonal antibodies and peptide

Monoclonal antibodies to the pretargeting approach: Developments in radiopharmaceuticals for RIT

The preventive study of gastric cancer peritoneal micrometastasis in nude mice with $^{188}$Re-labeled monoclonal antibody 3H11

Labeling of MoAb with $^{153}$Sm-HETA

The binding assay of $^{153}$Sm-EDTMP in vivo and in vitro

$^{153}$Sm complexes of phosphonate ligands

Influence of central metal ion on bone deposition of EDTMP chelates with different radionuclides

Trials to optimize dosimetry for $^{153}$Sm-EDTMP-therapy to improve therapeutic effects

Radiopharmaceuticals of DTPA, DMSA and EDTA labelled with Holmium-166

Studies on the preparation and evaluation of colloidal chromic phosphate - $^{32}$P for possible therapeutic use

MAG2GABA-Biocytin synthesized with new intermediates for radiolabeling $^{99m}$Tc and $^{188}$Re

Thursday 21 January 1999

Dosimetry in radionuclide therapy

Bone pain palliation with $^{32}$P therapy

32-Phosphorus for bone pain palliation due to bony metastases, its safety and efficacy in patients with advanced cancer

Therapy with strontium-89 for bone pain palliation in prostate cancer patients

New aspects of radionuclide therapy of bone and joint diseases

$^{166}$Ho-hydroxyapatite particles for radiation synovectomy

Radiation synovectomy with samarium-153 particulate hydroxyapatite: A preliminary report

Radiation synovectomy in chronic knee synovitis: Self experience and review of the literature

Rhenium radioisotopes for therapeutic radiopharmaceutical development

$^{188}$Rhenium-HEDP in the treatment of pain in bone metastases

Palliative effect of Re 186 HEDP in different cancer patients with bone metastases

Radiochemical studies and pharmacological behaviour of $^{186}$Re complexes of phosphonate ligands

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Invited Lecture I  
Monday 18 January 1999 : 10.00 - 11.00
Current trends in radionuclide therapy

Britton K.E.
St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK
Preparation of $^{90}\text{Y}$ and some preliminary results on labelling the radiofarmaceuticals

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The aim of the work was:
1. Preparation of new type of $^{90}\text{Sr}-^{90}\text{Y}$ generator with relatively high activity.
2. Separation of $^{90}\text{Y}$ with high radioactive concentration in chloride state and with high radiochemical and chemical purity for using in clinical practice for palliative treatment of skeletal metastases and for labelling antibodies, somatostatine, MDP, porphyrin etc for studying their properties as new potential radiopharmaceuticals for treatment soft tissue tumors.
3. Developing a new and fast method for evaluation the radiochemical and nuclear purity of elute of $^{90}\text{Y}$

I. Generator of $^{90}\text{Sr}-^{90}\text{Y}$

Generator of $^{90}\text{Sr}-^{90}\text{Y}$ was prepared by using $^{90}\text{Sr}$ as $^{90}\text{Sr} (\text{NO}_3)_2$ at 0.97M HNO$_3$. The ion exchange resin was Aminex-5 with a particle size $13 \pm 2 \text{ \mu m}$. The dimensions of chromatographic beds were $0.7 \times 5 \text{ cm}$. The generator was constructed with three chromatographic columns. The $\alpha$-hydroxyisobutiric acid ($\alpha$-HIBA) was used for elusion of $^{90}\text{Y}$ from the first two columns. The elusion process was controlled by measuring the bremsstrahlung of $\beta$-radiation of $^{90}\text{Y}$ by means of Nal(Tl) detector. 100 mCi of $^{90}\text{Sr}$ were loading on column.

Results

1. Elution process

The elution process is given in Fig. No 1. An efficiency of $^{90}\text{Y}$ elusion of 75-90% was observed in all experiments. These values are in accordance with published data for generators which were loaded only with relatively low $^{90}\text{Sr}$ radioactivity's ($\mu$Ci- up to few mCi level)

2. Radionuclidic and radiochemical purity

The main problem is a possible contamination of $^{90}\text{Y}$ by $^{90}\text{Sr}$. The $^{90}\text{Sr}$-breakthrough was measured by different methods as spectroscopy for the presence of trace of $^{85}\text{Sr}$, by measurement of $^{90}\text{Sr}$ by radiochemical separation from elute, decay curve of $^{90}\text{Y}$ and by a new developed method for fast chromatographic separation of $^{90}\text{Sr}$ from $^{90}\text{Y}$. We have get the content of $^{90}\text{Sr}$ radioactivity is less than 200 Bq per 85 mCi $^{90}\text{Y}$ or less than $5.4 \times 10^3 \mu$Ci/85 mCi $^{90}\text{Y}$. Radiochemical purity was checked by the original method following using ITLC method. Mobile phase was used 0.1M Tris (Tris-hydroxymethyl-aminomethan)
3. Trace elements as chemical impurities

According to Hnatovich et al. the effect of trace metals can be measured by testing the labelling yield on low concentrations of free DTPA in presence of $^{90}\text{Y}$. In our experiments have been used solutions of DTPA which were prepared with normal distill water and double distill water. In this case the difference are obviously. The results of these investigations are demonstrated at Tab. No 1.

**Table 1. Results of chromatography for the control of trace elements**

<table>
<thead>
<tr>
<th>DTPA-conc. [μmol/l]</th>
<th>Distilled water</th>
<th>Double distill water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of radioactivity Rf = 0</td>
<td>% of radioactivity Rf = 1</td>
</tr>
<tr>
<td>*25.4</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>2.54</td>
<td>2.5</td>
<td>97.5</td>
</tr>
<tr>
<td>0.254</td>
<td>11</td>
<td>89</td>
</tr>
<tr>
<td>0</td>
<td>99.7</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*1.0 μg / 100 μl

II. Preparing the yttrium citrate

The method of preparing of radiopharmaceutical $^{90}\text{Y}$-Citrate is relatively simple and fast. Radioactive $^{90}\text{Y}$-solution (activity depended on request) was added to 10 ml glass vial and was evaporated to dryness. After dryness to the vial was added 3 ml of isotonic solution (Concentration: 11.4 mM Na$_3$Cit*2H$_2$O and 77 mM NaCl) and was stayed for around 10 min to dissolve $^{90}\text{Y}$. Solution was filtered aseptically by using sterile sartorius membranfilter 0.22 μm. This solution is ready for using and is recommended to store it in refrigerator on 40°C. The radiopharmaceutical was used for treatment of pains from bone metastases in Oncology clinic of Tirana University Hospital Center.

III. Some problems in labelling of antibody

Mab B72.3 murine monoclonal antibody of the IgG$_1$ has been used for the labelling is directed against a high molecular weight tumor associated glucoprotein (TAG-72). For labelling properties antibody is conjugated with linker chelator glycyl-tyrosyl-N-e-diethylenetriamine penta acetic acid-lysine (GYK-DTPA). This is obtained in form of kit ONCOSCINT CR 103.

Solution of $^{90}\text{Y}$ (home made) was added to 1 ml solution of sodium acetate at pH 6. Desired activity from above mixture is added to vial with antibody and is let to stay at room temperature for incubation. The results obtained shows that the process of labelling is relatively fast (30 min). On the yield of labelling and in the results obtained play role some factors as pH, custom of analyses etc. Yield of labelling was obvious increased after pH 4.5

IV. Labelling methylene diphosponate (MDP)

MDP labelled with $^{99m}\text{Tc}$ has played a significant role in the diagnostic practice of nuclear medicine during last years. MDP and his substitute HO-MDP have a high accumulation in the bone metastases and fast blood clearance. In this background we undertook the study for labelling MDP with $^{90}\text{Y}$ as a potential radiopharmaceutical for therapeutic treatment of cancer metastases.
The complex $^{90}\text{Y}}$-MDP was prepared with satisfying yield and radiochemical purity more than 95%. By HPLC technique was studied the stability of complex. The complex was stable in vitro in water solution and in human serum and this stability was independent from the time of incubation and ratio of mixing sera-complex. Yield of labelling slightly depended from the conditions of performance of labelling such as pH, concentration of MDP and its quantity. It seems that pH had effected on the labelling and the lowest value of labelling was obtained in the band of pH 4-5.

References

Y-90 of high purity for clinical applications

Abmel Xiques Castillo¹, Keila Isaac Oliveré², Eunice Olivié Alvarez³
¹Isotope Center, ²High Institute of Nuclear Science and Technologies, CUBA

The Strellow [1] procedure described by Hnatowich [2] to free $^{90}$Y from excessive metal contamination (aspect to be taken into account when labelling antibodies) was studied and modified to work as well for purification of Y-90 from strontium-90 contamination.

The method briefly consists of making the elute from generator 0.5 M H$_2$SO$_4$ and pass it through an AG 50x8 (100-200 mesh) H$^+$ form resin. After washing with 0.5 M H$_2$SO$_4$ and 2 M HCl the $^{90}$Y is recovered with 4M HCl. A synthetic sample was prepared containing 0.003 M EDTA solution and 1 μCi of $^{90}$Sr/$^{90}$Y equilibrium solution and submitted to this purification process.

In figure #1 it can be observed that $^{90}$Sr is not separated from $^{90}$Y in the process and accompanies it to the end.

The modification introduced in the method consisted in adding a washing step with HNO$_3$ previous the elusion of $^{90}$Y with 4 M HCl. An other sample was then ran into the system and as appears in figure #2 both $^{90}$Sr and $^{90}$Y are separated from each other leaving first the column the $^{90}$Sr with the nitric acid and then the $^{90}$Y with the hydrochloric acid.

It is well known that $^{90}$Sr contamination levels increase in the elutes from $^{90}$Sr/$^{90}$Y generators with their ageing. In this study two generators of different activities and time of existence were used. The oldest one with 5 mCi activity and one and half a year old has been eluted irregularly varying the time between two consecutive elusions from 1 week to 3 months.
and the other one of 20 mCi is only six month old and has been milked regularly every week. Both generators were prepared following the method described first by Skraba [3] and more recently by Hnatowich where a Dowex 50x8 (50-100 mesh) resin in Na\(^+\) form serves as support and a 0.003 M EDTA (disodium salt) solution is used as eluant.

Several samples arising from the generators were analyzed and \(^{90}\)Sr contents determined by liquid scintillation employing the double energetic window method described by Moreno [4] and coworkers. The results of these analysis are shown in the following table:

**Table 1. \(^{90}\)Sr contamination levels in eluates from \(^{90}\)Sr/\(^{90}\)Y generators**

<table>
<thead>
<tr>
<th>eluate</th>
<th>date</th>
<th>(^{90})Sr/(^{90})Y ratio</th>
<th>generator #1 5 mCi</th>
<th>generator #2 20 mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18/04/97</td>
<td>((2.4 \pm 0.1) \times 10^{-5})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>21/04/97</td>
<td>((4.7 \pm 0.2) \times 10^{-6})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>30/04/97</td>
<td>((6.7 \pm 0.3) \times 10^{-6})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>28/05/97</td>
<td>((5.0 \pm 0.3) \times 10^{-6})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>27/06/97</td>
<td>((4.0 \pm 0.2) \times 10^{-6})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>01/07/97</td>
<td>((5.4 \pm 0.3) \times 10^{-6})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>21/08/97</td>
<td>((6.7 \pm 0.4) \times 10^{-6})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>17/07/98</td>
<td>((1.6 \pm 0.1) \times 10^{-5})</td>
<td>((3.1 \pm 0.2) \times 10^{-6})</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>23/07/98</td>
<td>((1.8 \pm 0.1) \times 10^{-5})</td>
<td>((8.2 \pm 0.4) \times 10^{-6})</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>08/08/98</td>
<td>((1.6 \pm 0.1) \times 10^{-4})</td>
<td>((2.9 \pm 0.1) \times 10^{-5})</td>
<td>-</td>
</tr>
</tbody>
</table>

In the case of generator #1 the content of \(^{90}\)Sr from sample #2 to sample #7 is in good agreement with the required values (\(^{90}\)Sr/\(^{90}\)Y ratio has to be kept below \(10^{-5}\) for in vivo use of the \(^{90}\)Y [5]). In the first eluate \(^{90}\)Sr contamination level is higher then in the next elutions due probably to the fact that only a small volume of eluant was used to wash the column immediately after loading the activity. The increase of \(^{90}\)Sr breakthrough in samples #8 to #10 is evident and correspond to elusions after a 3 months period of time in which elusion of the generator was not performed. In the case of generator #2 of higher activity only 3 samples have been measured but the content of \(^{90}\)Sr starts growing faster than in eluates from generator #1.

This procedure was applied to several samples from both generators. The purified \(^{90}\)Y was then used to label DTPA and measured to find its \(^{90}\)Sr content. In every case the efficacy of the method was proved by the increase in the percentage of DTPA labelling and the low values of \(^{90}\)Sr/\(^{90}\)Y ratios that were kept below \(10^{-6}\).

It is obvious that radiolysis damages the resin serving as support for generators causing their loss of capacity. This effect is increased chiefly with the increase of the loaded activity but also with the length of time passed between two consecutive elusions. Although generators used in this study have low activity, one must expect at higher ones the \(^{90}\)Sr breakthrough levels to grow even faster. So this modified procedure which can be used at laboratory scale brings the possibility to solve two problems at the same time: \(^{90}\)Y purification from metal contamination and from \(^{90}\)Sr. The latter is the most important parameter if it is intended for clinical use. Besides this procedure enlarges the usage of generators that not necessarily have to be dismantled when the degree of \(^{90}\)Sr breakthrough goes over the established limits.
Acknowledgments

The authors thank the IAEA's authorities that have supported this work through the CUB/2/011 project.

References


90Y and 105Rh labelled preparations: Potential therapeutic agents

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The potential of 90Y and 105Rh as therapeutic radionuclides has been realised since long [1-3]. Our attempts to prepare 90Y complexes, 90Y labelled ferrichydroxide macroaggregates and 105Rh-sulphur colloid are described in this paper. 90Y as chloride was from a 90Sr-90Y generator [4] while 105Rh-chloride was processed from irradiated Ru target [5]. The purity of 90Y and absence of 90Sr was ascertained by following the decay of the activity.

90Y complexes of DTPA (diethylene triamine pentaacetic acid), EDTMP (ethylene diamine tetramethyl phosphonate) and DOTA (1,4,7,10 tetraaza cyclododecane N,N',N'',N''' tetraacetic acid) were made under optimised reaction conditions of pH, time, reagent concentrations etc. 90Y-FHMA was made with an aim to use for radiation synovectomy. The complexes and the particulates were made under the optimised conditions to obtain the maximum labelling yield and the stability of the products were checked by the extent of leaching of 90Y activity with time, both in phosphate buffered saline (PBS, 0.04M, pH 7.5) and in human serum.

105Rh sulphur colloid was made with an aim to develop therapeutic agents for treatment by local administration both for radiation synovectomy and for hepatic carcinomas.

All the three ligands, DTPA, EDTMP and DOTA showed good complexation with 90Y. In all the cases, the complexation yields were determined by paper chromatography/TLC using pyridine : ethanol : water (1:2:4) elusion. DTPA complexed 90Y at a pH ~5.5 in acetate buffer to the extent of > 99% when the reaction was allowed to proceed at least for 2.5 h. A minimum of 1 µg of DTPA was required to complex trace amounts of 90Y (~0.2 picomoles). However, when the complexation was carried out with ~204 picomoles (18 ng) of carrier Y (which corresponds to 0.185 GBq of 90Y activity) the amount of ligand required was much higher at 80 µg corresponding to a ligand to metal ratio of 1000 : 1.

In the case of EDTMP, a much larger amount, 100 µg was required for complete complexation of trace amounts of Y and it was imperative to maintain the reaction pH at ~6-7. A cyclic phosphonate, tetraaza cyclo tetradecane N,N''N''',N''' tetra methylene phosphonate (CTMP), however, did not complex Y to appreciable extent under various reaction conditions, perhaps indicating the importance of the cavity size available for the complexation, which is observed with most metal ions including Y and several lanthanides.

As reported by several workers earlier, DOTA formed stable complexes with Y, at a pH ~5.5-6. Although very low amounts (say 0.2 µg) of DOTA, complexed 0.74 MBq of n.c.a. (no carrier added) 90Y, this required mild heating at ~ 40°C for ~ 30 minutes and the inter-batch variations were higher. With larger amounts of ligand, at 6000 : 1, the yields were consistantly high.

90Y labelled ferrichydroxide macroaggregates (FHMA) were prepared by precipitating the ferrichydroxide as fine particulates in presence of Y under alkaline conditions [6]. 78 ± 3 % of 90Y was labelled to the particles and no significant activity was lost on repeated washing with water, saline or buffer. 90Y did not leach out of the particles on storage in saline, phosphate buffered saline and human serum for upto 10 days.
$^{105}\text{Rh-S}$ colloid was prepared as reported for rhenium sulphur colloid [7]. 85 ± 4 % activity was associated with the colloid and as in the case of FHMA-$^{90}\text{Y}$, the particles were very stable and showed insignificant (< 3%) losses on washing and storage in buffer and human serum for upto 7 days.

References

Radiobiocjugate therapy: Silver and gold as candidate radionuclides - concepts and achievements


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Radiobiocjugate therapy comprises not only radioimmunotherapy but also the use of radiolabelled peptides, antisense nucleotides, radiolabelled hormones and other radiolabelled cell receptor specific ligands in the therapy of neoplasms.

With each of these modalities the choice of the warhead is critical and the possible warheads include Beta, Alpha and Auger emitter radionuclides. Halogenated immunoglobulins are widely used for in-vivo assays, but their use for radioimmunotargetting in-vivo is limited by the ubiquitous distribution of dehalogenase enzymes in-vivo even though the most widely used isotope in native form for therapy is I-131. P-32, Y-90, Cu-67, Re-186, Re-188 and Sm-153 are other attractive isotopes for open isotope therapy in general but their applicability for radioimmunotherapy in India is limited by various constraints. Our work on the possible use of the beta emitters Ag-111 and Au-199 for radioimmunotherapy is described as we were attracted [1] by their favourable $T_{1/2}$ of 7.45 days and 3.15 days respectively compatible with the temporal accumulation of antibodies in tumours and which also permits transport over large distances from reactors to users.

The Ag-111 has beta emissions EB 1.06 Mev (93%), 0.81 Mev (1%), 0.73 Mev (6%), along with useful gammas of 0.340 Mev (6%) and 0.243 Mev (1%). Au-199 has a beta emission of 0.30 Mev (70%), 0.25 Mev (24%) and 0.46 Mev (6%). It also has a useful gamma 0.158 Mev (41%) apart from two gammas of 0.209 Mev (9%) and 0.51 Mev (0.3%) and also some internal conversions. These gammas enable visualisation by the Gamma Cameras in clinical use. Most importantly both these isotopes can be prepared in practically carrier free form by the n-gamma process in a reactor. In collaboration with the Radiochemical Division of BARC we had standardised their preparation from Palladium and Platinum respectively.

46 mg Palladium chloride irradiated for 24 hrs in APSARA reactor at a flux of $1 \times 10^{12}$ neutrons/cm$^2$/sec, was applied to a 8% cross linked dry mesh 100-200 Dowex-1 anion exchange column pre-equipillbrated with 10M HCl followed by nine successive elutions. Silver (Ag) and Palladium (Pd) recovery were estimated by counting in a Ge-Li semiconductor multichannel analyzer (88 Kev channel for PD-100 and 245 & 342 Kev channels for Ag-111). Recovery of Ag was over 100% while 99.98% Pd was retained in the Dowex column.

For radiogold (Au-199), in order to obtain it in no carrier form Pt-198 (Platinum) irradiation method was chosen and 260 mg of Pt (99.9%) pure sample from Johnson Methy (U.K.) was irradiated in CIRUS reactor at a flux of $0.5 \times 10^{13}$ neutrons/cm$^2$/sec for 7 days in an aluminium can, later opened under reduced pressure and the irradiated powder dissolved in 10 ml Aque Regia in a radiochemical fumehood by gentle heating. Conc. HCl was added in aliquots to remove excess nitric acid and the volume reduced to 0.5 ml by gentle heating. This was taken up in 10 ml of 6M HCl and then extracted with pre-acidified ethyl acetate in a separating funnel. The HCl layer containing Pt in the form of chloroplatinic acid was discarded while the ethyl acetate extract containing Au-199 was distilled to obtain radiogold in the form of hydrochloroauric acid, 21 mCi of Au-199 being obtained without any significant platinum contamination.
Using silver for labelling antibodies presents considerable difficulties because of its monovalent nature and because of the very strong affinity of silver to the chloride ion which is widely distributed in vivo. Monovalent silver is difficult to link to conventional bifunctional chelates which have been used for linking Tc-99m or Y-90 to antibodies. Certain cryptates (Crown ethers) have been suggested as macrocyclic cages with a cavity in which the silver radiometal sits. Attempts to use these are at present limited by the very limited availability of such Crown ethers and necessity for their synthesis under stringent conditions [2]. We have therefore tried to exploit the silver-sulphur linkage in a soft acid-soft base interaction according to Schwarenbach classification. Apart from sulphur containing linkers such as SPDP, we hypothesised the linkage of silver to the sulphur naturally occurring in antibodies specially the cysteine elements. Encouraged by the Thakur de Fulvio technique [3] of linking Technetium to disulphide group in antibodies after ascorbic acid reduction, we successfully employed this eminently biocompatible agent to reduce antibodies for linkage with silver. In view of the short half life of Ag-111, pilot experiments were performed with radiosilver-110m as well as cold silver.

Further experiments were undertaken with 2-mercaptoethanol reduction as in the Schwarz [4] technique for Tc labelling of antibodies. Radiochromatogram shows successful linkage using above method. It was also possible to use exogenously introduced SH groups through 2-imino thiolane for linking silver to the antibody. The ethiol groups were titrated using 1.5 mM 2 2-Py-SS-Py prior to and after addition of silver. It was observed that depending on the concentration of silver, 50-80% of the SH groups were coupled to silver. Higher concentrations of silver led to insoluble precipitates and should be avoided.

Gold not being monovalent is relatively easier to link with antibodies. We have standardised the linkage of antibodies with antibodies. We have standardised the linkage of antibodies with Au-199 and improved [5] on the method of Anderson et al [6], which we found to be associated with a tendency for metallic Gold to be precipitated perhaps because of the citrate buffer used by them. On studying biodistribution in Swiss albino mice the gold labelled nonspecific immunoglobulin showed localization in the reticuloendothelial system and could be imaged as late as 4-5 days. Specific targeting of gold labelled immunoglobulins (anti-EGFR and M3 cytokeratin 18) in animals with tumors is under study experimental models of tumour being made by xenografting human tumours in immunosuppressed Swiss albino mice [7] as well as in nude mice obtained from Central Drug Research Institute, Lucknow. Apart from the tumour, gold labelled immunoglobulins are observed to accumulate in the liver, spleen, kidneys and large intestine. The native gold shows accumulation in liver and heart.

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The role of mathematical models in the optimization of radiopharmaceutical therapy

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Radiopharmaceuticals II
Production and radiochemical processing of therapeutic radionuclides

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The development of therapeutic radiopharmaceuticals involve research in a number of different areas. These include production and radiochemical processing of the isotopes, synthesis of ligands, complexation studies with radiometals, conjugation of the ligands complexes with carrier molecules and bio-evaluation in suitable animal models. The work carried out for the preparation of radionuclides for the development or therapeutic radiopharmaceuticals is discussed in this paper.

Most of the radioisotopes needed for medical applications in India are produced in the 100 MWt Dhruva reactor. The reactor has a large irradiation volume dedicated for the production of radioisotopes. The flux varies from 0.6-1.8 $\times 10^{14}$ neutrons/cm$^2$/sec. at full power operation.

Production of isotopes

$^{153}$Sm

$^{152}$Sm (n,γ) → $^{153}$Sm → $^{153}$Eu

$\sigma = 210$ b 47 h

Generally ~ 1 mg of Sm$_2$O$_3$ is irradiated for a week at flux of 3-6 $\times 10^{13}$ n/cm$^2$/sec. The irradiated target is dissolved in 0.5 M HCl solution. The specific activity of the product varies from 0.7-1 Ci/mg. The $^{153}$SmCl$_3$ solution prepared is used for complexation studies without any further processing.

$^{186/188}$Re

$^{185}$Re (n,γ) → $^{186}$Re → $^{186}$Os

37.7% 104 b 90 h

$^{187}$Re (n,γ) → $^{188}$Re → $^{186}$Os

62.93% 66 b 17 h

10 mg of Re metal (natural) is irradiated for one week and allowed to cool for 4 days. The target is dissolved in 2 M HNO$_3$ and treated with NH$_3$. The NH$_3$ReO$_4$ formed is extracted into MEK. the MEK layer is dried, dissolved in saline and used for complexation studies. The specific activity (~ 80 mCi/mg, 3 GBq/mg) of the product prepared is inadequate. However, with 7 day irradiation and one day cooling a product with adequate specific activity (221 mCi/mg, 8 GBq/mg) can be obtained. However, the product will have both $^{186}$Re and $^{188}$Re in a 60:40 ratio. As both $^{186}$Re and $^{188}$Re are isotopes suitable for therapy, we propose to develop a therapy protocol using this mixture.
$^{105}$Rh

$^{104}$Ru (n,γ) → $^{105}$Ru → $^{105}$Rh → $^{105}$Pd

18.58%; 0.7 b → 4.4 h → 35 h

100 mg of natural Ru is irradiated for one week and the target is dissolved in KIO₄ and KOH. RuO₄²⁻ is converted to RuO₄. Ru impurities are extracted with CCl₄ followed by a TBP extraction to remove $^{192}$Ir. The aqueous layer is further processed to get Rh in chloride form [1].

$^{166}$Ho

$^{165}$Ho (n,γ) → $^{166}$Ho → $^{166}$Er

100%; 65 b → 27 h

5 mg of Ho powder is irradiated for a week and target id dissolved in 1 N HCl and evaporated. The contents are dissolved in 0.1 N HCl and used directly.

$^{188}$W-$^{188}$Re Generator

1 g of WO₃ is irradiated for 4 months, dissolved in 3N NaOH and pH adjusted to 1.4 by addition of cone. HCl. 500 mg of ZrOCl₂ dissolved in 10 mL of DDW is added to this. Precipitated Zr-WO₄ is warmed gently to coagulate the precipitate. The precipitate is filtered, and crushed into smaller particles and loaded on a glass column. 6-7 mCi of $^{188}$W is produced and the $^{188}$ReO₄ yield is around 50% [2].

$^{90}$Sr-$^{90}$Y Generator

$^{90}$Y is separated from $^{90}$Sr using a generator, based on a supported liquid membrane. The feed solution of $^{90}$Sr (an aliquot from CMPO extraction at 2 M HNO₃) is taken in one of the compartments and the receiving compartment contains 0.5 M HNO₃.

Using the above radioisotopes a number of therapeutic radiopharmaceuticals have been developed or are under development. These include $^{153}$Sm-EDTMP, $^{186}$Re-(V)-DMSA, $^{186}$Re-HEDP, $^{166}$Ho labelled Hydroxy apatite (HA) and ferric hydroxide macroaggregates (FHMA).

References


Study on the preparation and stability of $^{188}$Re-biomolecules via EHDP

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A direct labeling technique via ethane-1-hydroxy-1,1-diphosphonic acid (EHDP) as a weak competing ligand was developed for the preparation of several biomolecules: $^{188}$Re-monovalent antibody for cell against carcinoembryonic antigen ($^{188}$Re-MoAb), biotinylated $^{188}$Re-MoAb ($^{188}$Re-MoAb-biotin), $^{188}$Re-polycyclonal IgG ($^{188}$Re-IgG), $^{188}$Re-peptide (somatostatin analogue peptide β-(2-naphthyl)-D-Ala-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-amide), $^{188}$Re-MoAb fragments ($^{188}$Re-F(ab')$_2$) and biotinylated $^{188}$Re-F(ab')$_2$ ($^{188}$Re-F(ab')$_2$-biotin). The reaction conditions such as pH, temperature, weak ligand concentration and stannous chloride concentration were optimized during the radiolabeling of each biomolecule. Before the labeling procedure, disulphide bridge groups of the biomolecules were reduced with 2-mercaptoethanol (2-ME). In the case of peptides, the radiolabeling was carried out using reduced and unreduced molecule. The general procedure for the preparation of $^{188}$Re-biomolecules was as follows: EHDP and 5 mg of gentisic acid were dissolved in 0.5 mL of stannous chloride solution (SnG$_b$ in 0.06 M MCl), and 1.0 mL of reduced or unreduced biomolecule was added followed by addition of 1.5 mL of $^{188}$Re-perrhenate solution (Oak Ridge National Laboratory).

The radiochemical purity for MoAb, F(ab')$_2$ and IgG was determined by a combination of instant thin layer chromatography (ITLC) and HPLC as reported previously [1]. The evaluation of the radiochemical purity for peptides was determined by ITLC-SG analysis (Table 1) and C-18 Sepak cartridges (Waters). The immunoreactivity of the labeled antibodies and its fragments was evaluated using affinity thin layer chromatography (ATLC) as Zamora et al reported [2].

Table 1. Systems employed during the determination of $^{188}$Re-peptide radiochemical purity by ITLC-SG analysis (1 x 10 cm strips)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>0.9 % NaCl</th>
<th>Acetone</th>
<th>Acidified ethanol (10 % HCl 0.01N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rf $^{188}$ReO$_4$</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Rf $^{188}$ReO$_2$</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Rf $^{188}$Re-peptide</td>
<td>0.0</td>
<td>0.7-1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Rf $^{188}$Re-EHDP</td>
<td>1.0</td>
<td>0.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

To obtain $^{188}$Re labeled antibodies and peptides in high radiochemical yields (>90%) via EHDP, it was necessary to use acidic conditions and a high concentration of stannous chloride to allow the redox reaction Re$^{7+}$ $\rightarrow$ Re$^{5+}$ : Re$^{4+}$ (Table 2).

Results showed that the immunoreactivity of the antibodies remains unaffected after the labeling procedure. However, MoAb and its fragments are unstable in vitro at neutral pH which is in agreement with the results obtained by other workers [3, 4]. These investigators have also found that the $^{188}$Re-MoAb complex is stable in vivo, may be due to a protective effect of serum proteins against the processes of $^{188}$Re reoxidation.
The labeling of MoAb and F(ab')₂ with \(^{188}\text{Re}\) via EHDP was also evaluated employing a pretargeted technique by avidin-biotin strategy in normal mice, demonstrating that the \(^{188}\text{Re}\)-labeled biotinylated antibodies are stable complexes \textit{in vivo}. The \(^{188}\text{Re}\)-peptide complex prepared by this method, was stable for 24 h and no radiolytic degradation was observed. In order to increase the radiochemical purity, a desalting column could also be used. However, this method is limited to labeling with \(^{188}\text{Re}\) only those peptides which contain cysteine bridges. The biological properties of the radiopeptides have to be evaluated since reaction condition are not an appropriate environment for their integrity.

\textbf{Table 2. Reaction conditions to label different biomolecules via EHDP.}

<table>
<thead>
<tr>
<th>Biomolecule</th>
<th>[SnCl(_2)] (mM)</th>
<th>[EHDP] (mM)</th>
<th>pH</th>
<th>Labeling time (h)</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{188}\text{Re}\text{-IgG})</td>
<td>0.88</td>
<td>30</td>
<td>3</td>
<td>18-22</td>
<td>22</td>
<td>98</td>
</tr>
<tr>
<td>(^{188}\text{Re}\text{-lgG})</td>
<td>3.52</td>
<td>120</td>
<td>3</td>
<td>0.5</td>
<td>37</td>
<td>97</td>
</tr>
<tr>
<td>(^{188}\text{Re}\text{-lgG})</td>
<td>7.04</td>
<td>120</td>
<td>4</td>
<td>2</td>
<td>37</td>
<td>97.5</td>
</tr>
<tr>
<td>(^{188}\text{Re}\text{-lgG})</td>
<td>7.04</td>
<td>120</td>
<td>5</td>
<td>18-22</td>
<td>22</td>
<td>97</td>
</tr>
<tr>
<td>(^{188}\text{Re}\text{-MoAb})</td>
<td>3.52</td>
<td>120</td>
<td>3</td>
<td>2</td>
<td>22</td>
<td>99</td>
</tr>
<tr>
<td>(^{188}\text{Re}\text{-MoAb})</td>
<td>3.52</td>
<td>120</td>
<td>3</td>
<td>0.5</td>
<td>37</td>
<td>98</td>
</tr>
<tr>
<td>(^{188}\text{Re}\text{-MoAb})</td>
<td>3.52</td>
<td>120</td>
<td>4</td>
<td>5</td>
<td>37</td>
<td>97</td>
</tr>
<tr>
<td>(^{188}\text{Re}\text{-MoAb-biotin})</td>
<td>3.52</td>
<td>120</td>
<td>3</td>
<td>0.5</td>
<td>37</td>
<td>96</td>
</tr>
<tr>
<td>(^{188}\text{Re}\text{-F(ab')}_2)</td>
<td>3.52</td>
<td>120</td>
<td>3</td>
<td>2</td>
<td>37</td>
<td>96</td>
</tr>
<tr>
<td>(^{188}\text{Re}\text{-F(ab')}_2\text{-biotin})</td>
<td>3.52</td>
<td>120</td>
<td>3</td>
<td>2</td>
<td>37</td>
<td>95</td>
</tr>
<tr>
<td>(^{188}\text{Re}\text{-peptide (reduced)})</td>
<td>11.76</td>
<td>120</td>
<td>3</td>
<td>1.5</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>(^{188}\text{Re}\text{-peptide (unreduced)})</td>
<td>11.76</td>
<td>120</td>
<td>3</td>
<td>1.5</td>
<td>92</td>
<td>90</td>
</tr>
</tbody>
</table>

\textbf{References}

Re-186 Bleomycin : Radiopharmaceutic for diagnosis and therapy?

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There is tremendous interest in developing of new radiopharmaceuticals for diagnosis and treatment of malignant diseases. Last decade development of beta emitting radiopharmaceuticals for palliative treatment of bone metastases is a good example of that [1]. Among other chemical compounds usefulness of bleomycin was investigated for diagnosis of malignant tumours. Cold bleomycin is a chemiotherapeutic agent used for therapy of malignant tumours. While labelled with Co57 [2], Tc99m [3] or In111 [4] and was used for scintigraphic diagnosis of different kind of tumors. There was different biodistribution and stability of radiolabelled bleomycin according to which radinuclide it was labelled. Though it was not widely used very promising results were obtained with Tc99m labelled bleomycin (BLM). It was rapidly cleared from the blood pool and taken up by neoplastic tumors. There were reports showing its usefulness for diagnosis of eye ball neoplastic diseases, breast cancer, neck tumours [5].

In this work we undertook the effort to label BLM with Re186. Re186 and Tc99m belong to the same group in periodic table. Re186 has a relatively short physical half-life of 90.64 h. It has both beta emission suitable for therapy (Emax = 1.07 MeV) and gamma emission suitable for external imaging (Eg = 137 KeV). Chemical properties of Tc99m and Re186 are similar so one can assume that probably methods of labelling and biodistribution of BLM-Re186 and BLM-Tc99m could be comparable as well. Labelling BLM with Re186 allow for obtaining the radiopharmaceutical suitable for radioisotope therapy of neoplastic tumours.

The aim of this work was to develop methods of BLM labelling with Re186.

There were the following methods used for labelling:
• conventional one with SnCl2,
• electrolytic,
• with the use cationit-Sn complex,

Natriumperr(Re186) MallinCrodt Medical , SnCl2 (Fluka), Dowex 1×8, Dowex 50×8, Dowex 50Wx4 in sodium or hydrogen form, 100-200 mesh Serva were used for labelling. The methods were the same as for BLM-Tc99m [5]. The products were analysed by thin layer chromatography on Silica Gel developed in a mixture of 10% CH3COONH4 : CH3OH (1:1 V/V). The yield of labelling by these three methods was very unsatisfactory.

Methods of HEDP-Re186 labelling were taken into consideration [6,7]. Gentisic acid (2,5-Dihydroxybenzoic acid) was used during the labelling and the reaction mixture was incubated at 100°C for 10 min.

In spite of changes in labelling procedure the yield of labelling by conventional method was still very poor. But by cationit-Sn complex method yield of labelling was 95%, by electrolytic method was 98%.

Authors showed that it is possible to label BLM with Re186. BLM-Re186 can be potentially a new agent for diagnosis and treatment of malignant tumours. Further investigations are carried out.
References


Rhenium-186 direct labeled IgG

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The aim of this study is to develop and improve existing radiolabelling techniques of peptides and monoclonal antibodies with $^{186}$Re for achievement of potential agents for cancer targeted radiotherapy.

We selected methods and techniques for the direct labelling of intact IgG by studying chemical and radiochemical processes of -S-S- bridges prereduction, reduction of $^{186}$ReO$_4^-$, and coupling reaction of rhenium with IgG.

The -S-S- bridges prereduction of IgG to sulfhydryls was effected using different reducing agents: ascorbic acid, 2,3 dimercaptopropanol, cysteine, active hydrogen. The prereduction reactions are controlled by masonic ratios of IgG/reduction agent, pH, temperature and time of incubation (see Table 1). A low acide pH and an incubation time of 24 hours are in the advantage of the prereduction yield.

<table>
<thead>
<tr>
<th>Reducing agent (RA)</th>
<th>(IgG:RA)/vol</th>
<th>pH</th>
<th>Incubation time (°C)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid</td>
<td>100 μg : 500 μg/200 μl</td>
<td>4</td>
<td>37</td>
<td>21 h</td>
</tr>
<tr>
<td>2,3 Dimercapto-propanol</td>
<td>100 μg : 64 μg/200 μl</td>
<td>3.5</td>
<td>22</td>
<td>22 h</td>
</tr>
<tr>
<td>Cysteine</td>
<td>100 μg : 120 μg/300 μl</td>
<td>4.5</td>
<td>37</td>
<td>22 h</td>
</tr>
<tr>
<td>Sn (7.5 mg) + citric acid (0.4 mg)</td>
<td>100 μg/300 μl</td>
<td>3.5</td>
<td>37</td>
<td>24 h</td>
</tr>
</tbody>
</table>

The reduction reaction of $^{186}$ReO$_4^-$ was effected with stannous chloride at acide and alkaline pH. The yield reducing for 370 MBq $^{186}$ReO$_4^-$ with 5 mg SnCl$_2$ x 2H$_2$O in 1 ml volume was between 92 - 96 %. The reducing time was 24 h at room temperature.

Each sample of IgG in prereduction form was labelled by two techniques:

a) by addition of 74 MBq $^{186}$Re in reduced form at pH = 5
b) by addition of 74 MBq Na$^{186}$ReO$_4$ in AA-IgG + 400 μg SnCl$_2$/chloride acid and AH - IgG + 400 μg SnCl$_2$/citric acid samples, pH = 3.5-4.5.

The results of radiochemical purity of IgG-$^{186}$Re, obtained by incubation for 1 hour and 22 hours respectively are presented in Table 2.

<table>
<thead>
<tr>
<th>IgG Samples</th>
<th>$^{186}$Re</th>
<th>Incubation time (h)</th>
<th>% Radiochemical purity ethanol</th>
<th>ethanol:NH$_3$H$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA - HlgG</td>
<td>74 MBq $^{186}$Re (red)</td>
<td>1</td>
<td>83</td>
<td>75</td>
</tr>
<tr>
<td>AH - HlgG</td>
<td>74 MBq $^{186}$Re (red)</td>
<td>1</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>AA - HlgG + SnCl$_2$</td>
<td>74 MBq $^{186}$ReO$_4^-$</td>
<td>22</td>
<td>93</td>
<td>87</td>
</tr>
<tr>
<td>AH - HlgG + SnCl$_2$</td>
<td>74 MBq $^{186}$ReO$_4^-$</td>
<td>22</td>
<td>95</td>
<td>96</td>
</tr>
</tbody>
</table>

The quality control was effected by chromatography techniques (paper and etution gel chromatography) on labelled IgG before and after purification. The elusion gel
chromatography was spectrophotometrically monitored at 280 nm. In the same time the radioactivity of samples was measured using a gamma counter.

All the results confirm in vitro stability of labelled IgG-\textsuperscript{186}Re. The biological evaluation studies regarding accumulation and biological affinity will be controlled by scintigraphy method. Biodistribution studies will be effected to bearing animals of Walker tumour at 4 and 24 hours after injections.

References

2. Eisenbut M. Preparation of \textsuperscript{186}Re - Perrhenate. *Int J Appl Rad Isot* 1982;33:99-103.
Therapeutic application of Holmium-166 Chitosan complex in the treatment of hepatocellular carcinoma

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²Korea Atomic Energy Research Institute, Taejon, KOREA

Holmium-166 is mainly beta emitter (Emax = 1.84 MeV, physical half-life = 26.8 hours) with 90% absorption in 2.3 mm of tissue and max. 8 mm in depth. As compared with Yttrium-90, it produces low gamma photon (0.081 MeV) that can be quantitatively imaged with gamma camera. On the other hand, Chitosan (1-4 linked 2-amino-2-deoxy-beta-D-glucopyranose) is a natural polymer which is polycathionic and biodegradable.

Holmium-166 chitosan complex (166Ho-CHICO) was prepared by reacting the aqueous acidic solution of chitosan with 166Ho(NO3)₃ at room temperature with quantitative labelling yield. The irradiation of 40 mg of 165Ho(NO3)₃ in a neutron flux of 1 x 10¹³ n/cm²sec. for 10 hours gave 100 mCi of 166Ho(NO3)₃.₅H₂O with radioactivity purity (> 99.9%). The process of the reaction and labelling yield were determined by instant thin layer chromatography using silicic acid impregnated glass fiber (ITLCSA) and developing solvent of MeOH:H₂O:HAC (49:49:2). The high labelling yield of more than 99% was obtained by reacting chitosan solution (35 mg / 4 ml) with 166Ho(NO3)₃ in which 7 mg of 165Ho+166Ho were contained as a maximum content. The labelling yield was highly dependent on the pH of the chitosan solution. The optimal labelling could be obtained at pH 2.5-3.5. The characteristics of 166Ho-CHICO were similar to those of chitosan, which is biocompatible, biodegradable, non-toxic, soluble and viscous in acidic condition but gelatinous at pH 6.0 and precipitating in alkaline conditions.

166Ho-CHICO can be easily prepared by reconstituting freeze-dried chitosan (kit A) with 166Ho(NO3)₃ solution (kit B) just prior to use. After intrahepatic administration of 166Ho-CHICO to male rats, the radioactivity concentration in blood were low and the cumulative urinary and fecal secretion over a period of 0-72 hours were 0.53% and 0.54% respectively. The radioactivity concentration in tissues and the whole-body autoradiography images showed that most of the administered radioactivity was localized at the administered site, and slight radioactivity was detected from the liver, spleen, lung and bones.

During the past 3 years, 166Ho-CHICO has been applying to treat hepatocellular carcinoma. The method was that 166Ho-CHICO solution is directly administered to target tumor under sonographic guidance just same as percutaneous ethanol injection (PEI). When the puncture of tumor was performed, 21 gauge commercially available needle with 4 side holes on the tip were used. Under watching TV monitor, the puncture needle was introduced to tumor and immediately administer 1-2 ml vol. contained the prepared 166Ho-CHICO and patients were transfered to gamma camera for confirmation of localized radioactivity. The dose was calculated by Monte Carlo code EGS4. More than one hundred patients has been treated by this method. The treated tumor ranged between 1.5 to 4 cm in diameter and less than 3 in number in one liver. The results are ; 86 % were treated successfully, 14% locally recurred during the period of one year follow-up. There was no clinically serious complications in all patients.

The benefit of this new therapeutic method over PEI is that it is painless and can reduce the frequency of injection. And also it can be monitored the undesirable radiation hazard by the immediate imaging on gamma camera. Recently we clinically began the intraarterial injection of
166Ho-CHICO to tumor supplying hepatic artery for the treatment of large hepatocellular carcinoma. The conclusion is that 166Ho-CHICO will be an effective and safe agent in the treatment of hepatocellular carcinoma.

Fig. 1a. CT scan: Contrast-enhanced hepatocellular carcinoma with 3.2 cm in diameter

Fig. 1b. Gamma camera scan: Well localization of radioactivity within tumor (Lt) and combined 99mTc phytate scan ( Rt) immediately 166Ho-CHICO administration.
Fig. 1c. MRI: Complete resolution of treated tumor 6 months after Ho-166 CHICO injection

References


Liver cancer as a model for radioimmunotargetting

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The liver can be involved in cancer in at least three different ways:

1. Hepatocellular Carcinoma
2. Cholangiocarcinoma
3. Metastases to the liver.

Hepatocellular carcinoma (H.C.C.) is one of the most important causes of morbidity in the world specially in South East Asia and in the Far East. A seven country I.A.E.A. comparative project on the estimation of Alfa feto protein as a tumour marker in subjects with liver disorders demonstrated a wide variation in the frequency of hepatocellular carcinoma in Thailand as compared to India and Greece and this study also demonstrated dramatic differences in the level of Alfa feto protein measured in these three countries. not only in the cases of hepatocellular carcinoma but also in the cases of portal cirrhosis and viral hepatitis, presumably reflecting a difference in the quantum of hepatitis B exposure [1]. Other factors such as Aflatoxins from contaminated ground nut or other food products for hepatocellular carcinoma or liver fluke infestations in the aetiology of cholangio carcinoma have been incriminated. Metastases to the liver considers a major problem during cancer management. While single metastases may be subjected to resection either by hepatectomy or gamma knife procedures, multiple metastases usually implies non operability.

This communication examines a number of options for radionuclide targetting in cancer of the liver and proposes this is as a model system for radionuclide therapeutic approach. As this is a difficult area for conventional surgery, chemotherapy as well as external teletherapy, Nuclear Medicine may make a meaningful contribution to the management of this problem.

Hepatocellular carcinomas secrete a large amount of Alfa feto proteins; there is also evidence suggesting alpha feto proteins receptors exist in diverse tumours. It is therefore logical to consider the use of radiolabelled anti Alpha feto proteins antibodies as well as possibly radiolabelled Alfa feto protein itself for the treatment of hepatocellular carcinoma.

Radiolabelled lipiodol has undergone extensive trials in the management of hepatocellular carcinoma but this approach requires locoregional approach of administration of lipiodol in the hepatic artery after angiography. Localized intra arterial injection of radiolabelled antibodies has also been attempted by Britton’s group [2] while evaluating 32-P labelled antibodies. While not underestimating the value of this logical approach. It is suggested that utilizing labelled antibodies it should be possible to obviate the need for intra arterial administration.

Metastases to the liver constitute another formidable problem in clinical oncology. In many instances the tumour arises from the gut and antibodies exist against them- e.g. colon cancer for which there are several existing antibodies e.g. PR A3 developed at ICRF, London.

In general, where the use of radiolabelled bio-conjugates against solid tumours is contemplated, the non specific uptake by the Reticuloendothelial system particularly the liver is considered a limiting factor, in part related to the Fc moiety of the antibody and to the Galactosyl residues present in the antibody. However we emphasize that in contrast to the
general problem, when treating liver metastases this so called disadvantage can be put to good use as the non specific targetting in the liver, if any, will contribute to the therapy of the metastases because of the neighborhood crossfire effect. A similar advantage exists in treatment of hepatocellular carcinoma.

Before trying these approaches in clinical practice it is obviously necessary to study this in experimental models. In order to do this experimental model was created injecting cancer cell lines intra hepatically both directly to the liver as well as in the portal vein or hepatic artery. After the creation of liver metastases have been confirmed, radiolabelled antibodies were injected in to the tail vein of the mice as well as intraperitoneally. Bio-distribution was measured both by serial scanning as well as in- vitro organ counting after sacrifice at timed intervals.

The results of these experiments with relative merits of the various methods of creating the models are discussed with data on bio-distribution of radiolabelled antibodies.

References

2. Britton K.E. Personal communication.
Experimental animal models for radioimmunotargeting

Pathak H, Hazra DK, Painuly NK, Watawana I, Gangwar PK, Khanna P, Gupta RK.
Nuclear Medicine and RIA unit. P.G. Dept. of Medicine, S.N. Medical College, Agra, INDIA

In order to study radionucleated therapy particularly in relation to radioimmuno-targeting, it is useful to utilize experimental models. Tumours arise spontaneously in certain animal strain. Further tumours can he induced by chemical carcinogens or by viruses. In addition human tumour can he xenografted in to mice. Since we were interested in eventual clinical use of our radiobioconjugates, we have utilized two different system for creating xenografts.

a. Using nude mice
b. Using immunosuppressed Swiss albino mice.

The relative merits of the two system are discussed on the basis of our experience for the last ten years.

As regards nude mice, these were obtained from the National Research Institute of Nutrition, Hyderabad, India, as well as Central Drug Research Institute, Lucknow, India. After a quarantine period of ten days the animals were subjected to tumour transplantation. In addition nude mice were locally bred. (Hairy heterozygous females with homozygous nude males). The animals were kept under stringent conditions of asepsis.

In the other system Swiss albino mice were immunosuppressed using 7 Gys Co 60 whole body irradiation and immunosuppressed by systemic intramuscular injection of 0.5 mg dexamethasone daily. If gastrointestinal infections were encountered they were treated by cotrimoxazole. Animals were also periodically dewormed by mebandazole.

Tumours were obtained from our hospital as well as other oncology centers. Tumour pieces were chosen from the non-necrotic non fungating area of the tumour at operation. Tumour pieces are collected in cold (4°C) transport medium (MEM) supplemented with Mycostatin, Streptomycin and Penicillin. These antibiotics and antifungals were added to prevent the contamination of the medium. The tissue pieces were carried to the laboratory with minimum time lag, after that tissues were left in RPMI/ DMEM tissue culture medium for 48 hours. After 48 hours, tissue pieces were implanted in the shoulder region as well as in the left thigh using sterile technique. Tumours developing here are easy to palpate and visualize and distinct from the liver and spleen region where non specific targeting occurs.

After 20-45 days the animals were imaged using radiolabelled antibodies or non-specific HIgG. The radioisotopes used in our laboratory are chiefly 131-I, 125-I, 199-Au, 198-Au and 99m-Tc. These animals are then subjected to gamma camera imaging. The imaging was performed at different time intervals spread over 8 to 10 days. The tumour region showed higher uptake compared to surrounding organs. The nature of the xenograft was confirmed histopathologically when animal was sacrificed.

It appears that more than 50% tumours were successfully grafted. These were derived chiefly from the breast and colon. The tumour bearing mice survived for two and half months. The advantage of the immunosuppressed model is as regards the cost of the system and the lesser requirement for stringent asepsis. However, the nude mice system has the advantage that it appears to be more akin to the human system. Other system has been described such as...
cheek pouch of the golden Hamster but we have no experience with them and we find both nude mice as well as immunosuppressed mice to be extremely convenient. So far as other methods of inducing cancer such as chemical carcinogens is concerned the results are not readily translatable to the clinical context because the immunological pattern may be quite different.
Therapeutic trials to control metastatic cancer with $^{90}$Y-DOTA-Lanreotide

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It is known that Lanreotide binds not only to Somatostatin receptors but possibly also to VIP receptors [1]. Therefore $^{90}$Y-Lanreotide could concentrate not only in carcinoids and similar tumors but also in tumors expressing VIP receptors. As therapy with $^{90}$Y-DOTA-Octreotide was introduced recently [2], we tried to treat metastatic cancer forms with uptake of $^{111}$In-DOTA-Lanreotide by infusion of $^{90}$Y-Lanreotide and report our first results.

**Material and methods**

Since December 1997 15 patients were treated. 8 had metastatic carcinoid tumors, 5 metastatic thyroid cancer without $^{131}$I-uptake (undiifferentiated or oncocytic carcinoma), 1 metastatic colon cancer and 1 cancer of the oesophagus. All patients initially had a whole body scan with 148 MBq $^{111}$In-Lanreotide with SPET on a double head gamma camera (Helix, Elscint). SPET data were analyzed on a Hermes workstation (NUD), data on biokinetics of the tracer were also followed by measuring activity in series of blood and urine samples over 3 days. If abnormal uptake of $^{111}$In-Lanreotide was found on scans the obtained data were used for dosimetry [3] with the aim to achieve with one application 3 Gy in the tumor. The selected patients then received 740 to 1590 MBq $^{90}$Y-Lanreotide in an infusion with saline and glucose over 2 hrs. This therapy were repeated after 2 - 6 weeks up to 6 times so that applied total activity was 1.850 to 4.400 MBq giving an estimated dose of 10 to 18 Gy to the tumor. After therapy patients were followed closely by clinical exam, blood analysis, urine analysis and imaging techniques to assess effects and side effects of therapy.

**Results**

Uptake of $^{111}$In-Lanreotide did not always correspond to uptake of $^{111}$In-Octreotide. While some tumors had more $^{111}$In-Octreotide uptake, others were seen better with $^{111}$In-Lanreotide on scans (Fig. 1). Results of therapy are shown in Table 1. Side effects where sometimes severe thrombopenia ($n = 5$) or moderate leukopenia ($n = 6$).

**Table 1. Results of Therapy with $^{90}$Y-DOTA-Lanreotide**

<table>
<thead>
<tr>
<th>tumor type</th>
<th>n</th>
<th>complete remission</th>
<th>partial remission</th>
<th>stable disease</th>
<th>progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid tumors</td>
<td>8</td>
<td>-</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Oesophagus Ca.</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon + prostate Ca.</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid Ca.</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Overall</td>
<td>15</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

**Discussion**

Therapy with $^{90}$Y-Lanreotide was primarily planned for metastatic carcinoid tumors. This disease responds well to therapy with $^{90}$Y-DOTA-Octreotide. We found, however, uptake of Lanreotide also in other tumors (colon, thyroid) which responded to therapy with $^{90}$Y-DOTA-
Lanreotide well in several cases. In the future it will be essential to determine receptor expression in different cancer types by scanning with appropriate by labeled peptide receptor ligands and to decide then which $^{90}$Y-labeled receptor ligand should be used for therapy. Precise dosimetry will remain essential for planning therapy with such compounds. Our preliminary results show, that therapy with $^{90}$Y-labeled receptor ligands could become an important progress in management of various forms of metastatic cancer, in which other therapeutic modalities have failed.

**References**

Pirocarbotrat™: a new radiopharmaceutical labeled with $^{32}\text{P}$ for the treatment of solid tumors.
Therapeutic action and radiodosimetric calculations.

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$^3$Pathology Service, Mater Dei Sanatorium, Buenos Aires, ARGENTINA

Pirocarbotrat™ is a gelatin protected charcoal suspension labeled with chromic $^{32}\text{P}$ pyrophosphate. To evaluate its effectivity as a therapeutic agent for the treatment of solid tumors, studies of therapeutic action and dose calculations, were carried out after an intratumoral single dose of this radiopharmaceutical.

The preparation of the Pirocarbotrat™ (BACON Laboratories) was described elsewhere [1, 2]. We used 28 female Sprague Dawley rats in which experimental mammary adenocarcinomas were induced. The tumors were injected with a single dose of 18.5 MBq. The size of the injected and not-injected tumors (controls) was determined with a caliper along two axes as a function of time. Once the experiment was finished, animals were sacrificed to extract their organs and the injected tumors. The radioactivity of the samples as well as a $^{32}\text{P}$ standard (18.5 MBq) were measured in a monochannel gamma spectrometer, using the Bremsstrahlung photons of $^{32}\text{P}$. Representative pieces of tissues from the treated and control tumors were selected for histopathological examination. The histological findings were evaluated according the type and degree of local response to the radiopharmaceutical, concerning the neoplasia and the nonneoplastic surrounding tissue.

The results show that after 32 days of treatment, the percentage of activity found in the tumor was $84.50 \pm 2.60\%$, while the percentage of activity found in the other evaluated organs was almost negligible as it can be observed in Figure 1 [1].

![Fig. 1. Biological distribution of Pirocarbotrat™ after 32 days of treatment.](image)
The therapeutic action was evaluated by the mean size ratios (M.S.R.) defined as the tumor size at the last day of life / tumor size at the day of the injection and the percentage of tumor regression (P.T.R.) which was 0.6 ± 0.3 and 78.3%, respectively. Our histological observations were carried out 32 days after the injection, i.e., once 80% of the $^{32}$P radioactivity was delivered to and absorbed by the tumor. The treated tumors showed closely packed black charcoal particles at the injection point, which are shown always in sharply demarcated big clusters and always associated with necrotic debris from the neoplastic tissue. Nearby the border of the cluster variable tumor necrosis can be observed as well as reparative changes arising from the surrounding normal tissues that replace the necrotic areas progressively. The extension of the necrotic tissue in the tumor vicinity is variable, ranging from 1 to 4 mm. Radiodosimetric calculations demonstrate that the dose absorbed by the tumors was 6190 Gy, according to the Medical Internal Radiation Dose Committee (MIRD) of the Society of Nuclear Medicine. The dose absorbed by the rest of the organism is 0.533 Gy. The rate dose to the tumor/dose to the rest of the organism is $1.17 \times 10^4$. These results might be explained due to a low mobilization of the radiopharmaceutical from the injection point, which allows to deliver a high radiation dose to the tumor provoking a consequent tumor size reduction, confirmed by the histopathological findings, where it is clearly demonstrated that the Pirocarbotrat™ particles remain closely packed and do not move from the injection point.

The therapeutic efficiency of Pirocarbotrat™ is due to its low mobilization and its high concentration in solid tumors. This behavior allows the delivery of high doses to the tumor, with low irradiation to surrounding tissues and organs. Irradiation to the rest of the organism is insignificant. We can conclude that, Pirocarbotrat™, a non-sealed beta radiation source, behaves very closely to a sealed beta radiation source when it is intratumorally injected in solid tumors.

References


Management of thyroid cancer with I-131: An overview

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Radioiodine therapy in management of thyroid carcinoma -
A review of 138 patients

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Bangladesh Atomic Energy Commission, Dhaka, BANGLADESH

Thyroid cancer is the commonest endocrine malignancy, yet management remains continually controversial [1]. Differentiated thyroid carcinoma are being treated by using a widely accepted protocol of surgery and radioiodine therapy followed by supplementation of thyroid hormones. The efficiency of this approach has been well documented [2] In the Nuclear Medicine Centre (NMC) of Dhaka Medical College Hospital (DMCH) this method has been successfully practiced in collaboration with surgeons and considered as a major part of the management of differentiated thyroid cancer since 1990. In the present study the management of a total of 138 patients (54 male, 84 female) with differentiated thyroid cancer has been reviewed covering the period of January 1990 to December 1997.

Some of these patients were reported to NMC, DMCH, Dhaka in pre-surgical state for initial diagnosis who were then evaluated by ultrasonography, in vivo and in vitro nuclear medicine techniques and final diagnosis was documented by histopathology during or after operation. In most instances a total or near total thyroidectomy was performed at the time of the first operation or as a second procedure following total thyroidectomy usually a period of 4 weeks were allowed to elapse with a view to permit serum TSH to rise before a large dose scan was performed [3].

All the patients were subjected to post operative evaluation by I-131 scanning for residual thyroid mass and metastases - if any. Initially 3.7 MBq (100 µCi) of I-131 was orally administered for screening at 24 hours. Specially in cases of hemithyroidectomy or lobectomy, it has been observed that significant amount of residual thyroid tissue remained intact and in those cases I-131 ablation therapy was instituted immediately [4] with an average dose of 75-100 mCi. In cases of lymph node mets about 175 mCi, in lung mets about 150 mCi and in bony mets in an average 200 mCi doses were applied.

In subsequent follow up I-131 large dose scan S. Thyroglobulin estimation were usually performed at six monthly or yearly intervals with repeated I-131 therapy until tumor ablation was attained. Among 138 patients, papillary carcinoma was observed in 94 cases (male 42, female 52), follicular type carcinoma was observed in 30 patients (male 8, female 22) while mixed type carcinoma (papillary-follicular) was observed in the rest 14 cases (male 4, female 10). Regarding dose application, all 38 patients initially received single dose (75 - 100 mCi I-131), consequently 62 received two doses (total 250 mCi), 44 received three doses (total 350 mCi) and only one patient received an exceptionally large number of doses i.e. 8 doses (900 mCi). Regarding efficacy of the doses, it has been observed that single dose in 138 cases yielded complete ablation in 76 cases while 62 remained unablated. All unablated patients were given multiple doses and finally all ablated except 34 patients are still unablated and under follow up. The success and failure in management of patients with differentiated thyroid cancers over 8 years period has been discussed here revealing a satisfactory outcome.
Table 1. Types of surgery and doses needed for ablation.

<table>
<thead>
<tr>
<th>No. of doses</th>
<th>Total thyroidectomy</th>
<th>Near total thyroidectomy</th>
<th>Hemi-thyroidectomy</th>
<th>Sub-total thyroidectomy</th>
<th>Extended thyroidectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>14</td>
<td>26</td>
<td>2</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Multiple</td>
<td>4</td>
<td>8</td>
<td>36</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. Outcome of 138 thyroid carcinoma patients receiving radioiodine therapy for ablation.

<table>
<thead>
<tr>
<th>No. of dose</th>
<th>No. of cases</th>
<th>Ablated</th>
<th>Unablated</th>
<th>Total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>138</td>
<td>76</td>
<td>62</td>
<td>~ 75 - 100 mCi</td>
</tr>
<tr>
<td>Two</td>
<td>62</td>
<td>18</td>
<td>44</td>
<td>~ 250 mCi</td>
</tr>
<tr>
<td>Three</td>
<td>44</td>
<td>10</td>
<td>34</td>
<td>~ 350 mCi</td>
</tr>
<tr>
<td>More than three</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>~ 900 mCi</td>
</tr>
</tbody>
</table>

References

Treatment of thyroid cancer with I-131 at INMOL, Lahore

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Institute of Nuclear Medicine and Oncology, Lahore, PAKISTAN

A total of 354 patients were registered with us from 1985 to 1997. A predominant majority comprised of female (72%) while only 27% were males. Maximum incidence was in the 5th decade of life followed by the 4th, 6th and 3rd & 7th. Below 20 years of age the incidence was only 3.95% & it became sparse again beyond the age of 70 years. Histologically papillary carcinoma was the commonest sub type. Follicular was the 2nd in prevalence followed by anaplastic medullary & undifferentiated (2.8%). Mixed follicular & papillary variety comprised 19%. Majority of the patients came to us after surgery which was sub total thyroidectomy in 33%, near total thyroidectomy in 22% of cases. 3.1% came to us following radical thyroidectomy while 20% after pential laboratory isthaemectomy. 27.4% came after non radical surgery like FNA. Excision biopsy, lymph node biopsy, cold nodule excision. 92% of our patients were from Central Punjab, 6.2% from South of Punjab & 0.5% from the Potohar Region. Patients from the Northern areas comprised only 1.4% of our total cases. 52% were in stage-II, 24.5% in stage-III, 14% in stage-IV & only a small percentage of 4.77 in stage-I. Commonest site of metastasis in stage-IV cases was bone, followed by jung, lymph nodes & in 0.5% metastasis was scan in the liver. For I\textsuperscript{131} treatment 100 mCi was given once to 41% patients. In 17.5% patients I\textsuperscript{131} 100 mCi was given more than once. In 12.4% patients 100 mCi was follow by a high dose. < 100 mCi was given once to 1.4% while < 100 mCi dose had to be repeated more than once in 9.8%. > 100 mCi was given once in 8.2%. The role of radiotherapy was limited to patients with anaplastic & medullary carcinoma or for palliative reasons to 9.3% patients. In our study 20.3% patients of anaplastic & medullary CA received Radiotherapy. Chemotherapeutic agents used were Adriamycin, Cisplatinum & Epirubicin. It was given for anaplastic CA in 1.4% cases in 0.27% patients of medullary carcinoma & in 0.5% patients with recurrence. 55.3% patients continued to follow us up for 1 year. 24.8% were followed for 2 years. 3.1% patients expired. Longest follow-up seen was for 7 years in 0.8% of our patients. 15.8% were lost to follow-up.
Radiation dose rates from patients receiving iodine-131 therapy for carcinoma of the thyroid in 1997 and 1998 at I.P.O.F.G. in Lisbon

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Medicina Nuclear I.P.O.F.G. Lisboa, PORTUGAL

The Nuclear Medicine Department of the Instituto Português de Oncologia (I.P.O.F.G.) has a large experience using 131-I for therapy, both in thyrotoxicosis and thyroid cancer. In fact, we have used 131-I for thyroid therapy since 1950 and a thorough continuous work has been carried out. Since 1993, we have been measuring the radioactive dose rate of the patients who had therapy for thyroid carcinoma, immediately before discharge. The measurements have been performed with a dose ratemeter - Berthold LB 133 - directed to the thyroid region of the patients, at a distance of 0.1, 0.5 and 1 metre. This work will focus on the analysis of the measured values from January 1997 until July 1998. We analyzed the data of a total of 248 patients (pts). 150 pts received 2.59 GBq of iodine-131 for ablation of residual thyroid after surgery (ablation group) and 98 pts received 4.18 GBq for residual or recurrent disease (follow-up group). All those pts had to stay in the hospital for some days, usually three days for ablation group and four days for follow-up group. The dose rate measurements of the patients before discharge aimed firstly to validate the hospitalization periods of the patients (which were fixed until now only by local organizational reasons). Secondly, these measurements are an attempt to provide the basis to define the recommendations to be given to the patients before leaving the hospital, in order to guarantee that the annual limit effective dose (1 mSv) [1] will not be exceeded in bystanders and reduce, as much as possible, their exposure to radiation. Furthermore, the values allow us to indicate how long the precautions are to be taken. These instructions typically include [2]:

1. sleep in separate beds:
2. avoid close and/or prolonged contact with others especially children and pregnant women:
3. delay return to work:
4. avoid public transportation:
5. limit the time spent in public places.

To cover all those situations we decide to perform the measurements at 0.1 0.5 and 1 metre corresponding to common distances found between the patient and family members or other bystanders (e.g. at work, in public places). Despite the fact that legal regulations regarding the discharge of the patients do not exist in Portugal we try to give instructions [2] to these patients to minimize radiation hazards to the public, i.e., to prevent exposure and contamination of the public. In a previous work presented as a poster at the 1995 EANM Congress [3] we had defined a safety limit for the dose rate value which would assure the safety of the exposure of bystanders and we calculated the periods of restriction to be observed by the patients according to the values measured at discharge time. To found the instructions given to the patients before leaving the hospital, dose rate calculations were performed based on the assumption that the exposure dose must not exceed the annual limit (1 mSv), for various number of hours of daily exposure taking into account the different periods of time bystanders would spend with the patient. Table 1 shows the comparison of dose rate values (µSv/h) measured on 3rd day and on 4th day during 1997 (87 and 9 pts) and 1998 (39 and 16 pts) for ablation group. Table 2 presents the comparison between the values measured (µSv/h) in 1997 (85 pts) and 1998 (13 pts) on 4th day for patients of follow-up group.
Table 1. Ablation group

<table>
<thead>
<tr>
<th></th>
<th>10 cm mean</th>
<th>10 cm stdev</th>
<th>50 cm mean</th>
<th>50 cm stdev</th>
<th>100 cm mean</th>
<th>100 cm stdev</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>115.9</td>
<td>183.6</td>
<td>17.6</td>
<td>20.1</td>
<td>7.2</td>
<td>8</td>
</tr>
<tr>
<td>1998</td>
<td>90.7</td>
<td>115</td>
<td>14.4</td>
<td>15.6</td>
<td>5.8</td>
<td>5.3</td>
</tr>
<tr>
<td>P(t)</td>
<td>0.18</td>
<td>0.176</td>
<td>0.091</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4th day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>23.3</td>
<td>20.4</td>
<td>4.6</td>
<td>4.1</td>
<td>2.2</td>
<td>1.5</td>
</tr>
<tr>
<td>1998</td>
<td>58.9</td>
<td>57.8</td>
<td>13.1</td>
<td>12.2</td>
<td>5.4</td>
<td>5.1</td>
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<tr>
<td>P(t)</td>
<td>0.017</td>
<td>0.009</td>
<td>0.014</td>
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</tr>
</tbody>
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Table 2. Follow-up group

<table>
<thead>
<tr>
<th></th>
<th>10 cm mean</th>
<th>10 cm stdev</th>
<th>50 cm mean</th>
<th>50 cm stdev</th>
<th>100 cm mean</th>
<th>100 cm stdev</th>
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<tbody>
<tr>
<td>4th day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>29</td>
<td>69.5</td>
<td>7.1</td>
<td>8.7</td>
<td>3.3</td>
<td>3.7</td>
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<tr>
<td>1998</td>
<td>28.6</td>
<td>33.8</td>
<td>8.6</td>
<td>9.6</td>
<td>4.8</td>
<td>4.9</td>
</tr>
<tr>
<td>P(t)</td>
<td>0.485</td>
<td>0.411</td>
<td>0.165</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From the observation of these tables we conclude that the values measured on 3rd day for ablation group in the two years can not be considered statistically different (t-Student; \( \sigma = 0.01 \)) and similarly for the 4th day values of follow-up group, permitting the joining of the two samples corresponding to different years as one unique sample. The values measured on 4th day for ablation group are a very small sample and this can explain the low values of the probability (Table 1). Despite the differences found in the dose rate values from patient to patient in each group the frequency distribution of values are rather normal in each sample. Another aspect analysed was the validation of the internal rule in our Department regarding the periods of hospitalization. On Table 3 we present the comparison of values measured for the two groups on 4th day. The two populations, quite different in size, can not be considered statistically different. We also tried to perform the comparison between populations more similar in size and we applied a correction of one day physical decay to the values of ablation group measured on 3rd day. For those values we found a difference highly significant, but the correction only by physical decay can be excessively smooth [4] and it is impossible to decide between the two groups which must stay longer. Any way, in any group the values measured at 1 metre are low enough to allow the discharge of the patients in safe conditions. Comparing the values measured at the three distances for each patient with the “safety limit” enable us to precise the recommendations to apply to the bystanders and to advice the respective periods of restriction.

Table 3.

<table>
<thead>
<tr>
<th></th>
<th>10 cm mean</th>
<th>10 cm stdev</th>
<th>50 cm mean</th>
<th>50 cm stdev</th>
<th>100 cm mean</th>
<th>100 cm stdev</th>
<th>no. patients</th>
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<tr>
<td>Ablation</td>
<td>46.1</td>
<td>49.4</td>
<td>10.2</td>
<td>10.6</td>
<td>4.2</td>
<td>4.3</td>
<td>25</td>
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<tr>
<td>Follow-up</td>
<td>61.8</td>
<td>65.7</td>
<td>18</td>
<td>8.8</td>
<td>5.4</td>
<td>3.9</td>
<td>98</td>
</tr>
<tr>
<td>P(t)</td>
<td>0.158</td>
<td>0.214</td>
<td>0.452</td>
<td></td>
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Table 4.

<table>
<thead>
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<th>100 cm</th>
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<th>no. patients</th>
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<tr>
<td></td>
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<td>mean</td>
<td>stdev</td>
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<tr>
<td>Ablation</td>
<td>95.7</td>
<td>149.5</td>
<td>15.2</td>
<td>17.2</td>
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<td>6.7</td>
<td>125</td>
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<tr>
<td>Follow-up</td>
<td>61.8</td>
<td>65.7</td>
<td>18</td>
<td>8.8</td>
<td>5.4</td>
<td>3.9</td>
<td>98</td>
</tr>
<tr>
<td>P(t)</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
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</table>

References

What should be the optimal dose of $^{131}$I for remnant ablation in differentiated thyroid cancer?

Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, INDIA

Abstract

Radioiodine has been used for more than half-century to ablate thyroid remnants following thyroid surgery, but a single optimal $^{131}$I therapy dose or radiation absorbed dose has not been established. To establish the optimal dose we evaluated 149 patient files who had undergone remnant ablation at AIIMS. Methods: In this prospective study 149 patients with only remnant thyroid were randomised into four treatment groups. 27 patients found in 25-35mCi range, similarly 54 in 35-64 mCi, 38 in 65-119 mCi and 30 patients in 120-200 mCi range. All subjects were reassessed after withdrawing L-thyroxine for 4-6 weeks. The absorbed radiation dose was calculated according to the equation described by Maxon et al. The mass of the remnant tissue and the effective half-time were assumed as described by Snyder et al.

Results: Applying the above criteria we observed complete ablation of 17/27 (63%) in 30 mCi group, 42/54 (77.8%) in 50 mCi group, 28/38 (73.7%) in 90 mCi group and 23/30 (76.7%) in 155 mCi group. When radiation absorbed dose was calculated a 30 mCi dose delivered approximately 20,000 cGy, 50 mCi about 30,000 cGy, 90 mCi about 50,000 cGy and 155 mCi about 130,000 cGy. Conclusion: We conclude, increasing the $^{131}$I initial radiation absorbed dose beyond 30,000 cGy or giving >50 mCi results in plateauing of dose-response curve and unwanted whole body dose. Thus, conventional high dose remnant ablation needs critical evaluation, as higher doses does not appear to yield a higher ablation rate.

Introduction

Ablation of functioning residual thyroid tissue after adequate surgery by radioiodine is somewhat controversial considering the indolent nature of well differentiated thyroid carcinoma [1, 2]. The first, of course is whether the remnant tissue should at all be ablated or not? The second controversy is regarding the optimal dose of $^{131}$I required to achieve a successful ablation. A variable success rate ranging from 0 to 90% have been reported with empirical low dose therapy [3-5]. The third controversy is defining the successful ablation itself. Maxon and his colleagues believe the dosimetric approach is an ideal method for remnant ablation and have proposed a threshold level for dose response [6-7]. Contrary to this, Snyder et al have severely criticise the basis of this dose calculation and refute the concept of threshold dose [8]. Samuel and Rajahekkharrao have emphasized the importance of initial dose rate, not cumulative dose, as a critical factor for thyroid remnant ablation [9]. However, there was no prospective randomized clinical trial available in the literature to substantiate or refute these arguments. We have conducted a prospective randomized clinical trial to find out the optimal dose of $^{131}$I for remnant tissue ablation, using a variable administered dose schedule.

Methods

Using a simple randomization technique 149 eligible patients with only remnant thyroid were incorporated into four treatment groups (Table 1). Twenty-seven patients were administered 25-34 mCi (30 ± 1.5), 54 received 35-64 mCi (50.6 ± 5.4), 38 received 65-119 mCi (88.6 ± 14) and 30 patients received 120-200 mCi (155 ± 28.7) of $^{131}$I. The absorbed radiation dose was calculated according to the equation described by Maxon et al [7].
Thyroid Cancer I

\[ D (\text{rad}) = \frac{\hat{A}}{m} \sum \Delta_i \Phi_i = C_0 1.44 (T_{1/2})_{\text{eff}} [0.4135 + 0.8041 \Phi_i] \]

where \( \hat{A} (\mu\text{Ci-hr}) \) is the cumulated activity; \( m (\text{g}) \) is the mass of the lesion, \( C_0 (\mu\text{Ci/g}) \) is the initial radionuclide concentration in the lesion, \( (T_{1/2})_{\text{eff}} (\text{hr}) \) is effective half-time in the lesion, \( \Delta_i (\text{g-rad/\muCi-hr}) \) is the equilibrium dose constant, and \( \Phi_i \) is the absorbed fraction. The mass of the remnant tissue and the effective half-time were assumed as described by Snyder et al [8].

Six month to 1 year after treatment, all subjects were reassessed after withdrawing L-thyroxin for 4-6 weeks. A successful ablation was defined as the absence of thyroid bed activity in 5 mCi \( ^{131} \text{I} \) neck scan at 48 hours along with two adjunctive criteria which were the neck uptake of < 0.2% of the administered activity and thyroglobulin (Tg) value of < 10 ng/dl. A stepwise logistic regression analysis using successful ablation (or not) as dependent variable and age, sex, type of surgery, histopathology and individual \( ^{131} \text{I} \) administered activity as explanatory or predictor variable was performed using BMDP package.

### Table 1. Demographic Profile of four randomized patient groups

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>25 - 35 mCi</th>
<th>35 - 64 mCi</th>
<th>65 - 119 mCi</th>
<th>120 - 200 mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of Pt.</td>
<td>27</td>
<td>54</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>Age in Yr (Mean)</td>
<td>38</td>
<td>37</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>Female:Male</td>
<td>20:7</td>
<td>42:12</td>
<td>23:15</td>
<td>19:11</td>
</tr>
<tr>
<td>HPE (Pap:Follicul)</td>
<td>22:5</td>
<td>28:26</td>
<td>18:20</td>
<td>19:11</td>
</tr>
<tr>
<td>Type of Surgery (NTT : Subtotal)</td>
<td>26:1</td>
<td>45:9</td>
<td>30:8</td>
<td>21:9</td>
</tr>
<tr>
<td>Pre-Ablation RAIU at 48hr</td>
<td>6.6%</td>
<td>6.2%</td>
<td>5.6%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Range</td>
<td>2.0 - 15.6%</td>
<td>1.6 - 19.8%</td>
<td>3.5 - 12.4%</td>
<td>1.8 - 17.7%</td>
</tr>
</tbody>
</table>

HPE = Histopathology, pap = Papillary Carcinoma, Follicul = Follicular Carcinoma
NTT = Near total thyroidectomy, RAIU = Radioactive iodine-131 uptake

### Results

Applying the above criteria we observed complete ablation of 17/27 (63%) in 30 mCi group, 42/54 (77.8%) in 50 mCi group, 28/38 (73.7%) in 90 mCi group and 23/30 (76.7%) in 155 mCi group(Table2). When radiation absorbed dose was calculated a 30 mCi dose delivered approximately 20,000 cGy, 50 mCi about 30,000 cGy, 90 mCi about 50,000 cGy and 155 mCi about 130,000 cGy. The adequacy of surgery was an important prognostic factor that influences the remnant ablation, surprisingly \( ^{131} \text{I} \) administered activity had no effect on the same.

### Table 2. Radioiodine Ablation Results in Various groups

<table>
<thead>
<tr>
<th>Various Groups</th>
<th>25 - 35 mCi</th>
<th>35 - 64 mCi</th>
<th>65 - 119 mCi</th>
<th>120 - 200 mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity (mCi)</td>
<td>30.0 ± 1.5</td>
<td>50.6 ± 5.4</td>
<td>88.6 ± 14.0</td>
<td>155.0 ± 28.7</td>
</tr>
<tr>
<td>Radiation absorbed dose (cGy)</td>
<td>19,800 ± 992</td>
<td>31,372 ± 3355</td>
<td>49,616 ± 7858</td>
<td>130,200 ± 24,162</td>
</tr>
<tr>
<td>Successful ablation (in percentage)</td>
<td>17/27 (63 %)</td>
<td>42/54 (77.8 %)</td>
<td>28/38 (73.7 %)</td>
<td>23/30 (76.7 %)</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± sd. Statistical analysis of patient characteristics
such as age, sex, percentage uptake, type of surgery and histopathology between two groups, those who had ablated and those failed, revealed no significant difference by chi square test.

**Discussion and Conclusion**

McCowan et al in 1976, reported that doses of 80-100 mCi were not more effective than 30 mCi [10]. Subsequently, prospective studies confirmed similar finding [11-12]. The interest in administering the smallest effective dose of $^{131}$I is the advantage of out-patient treatment with the attended economy and convenience. There is also theoretical advantage of decreasing the risk of leukaemogenesis and extrathyroidal organ damage from lower whole-body radiation specially in young patients with favorable prognostic factors [13]. Per Hall et al from Sweden reported the risk of second primary cancer in patients who have been treated with $^{131}$I and compared with that of age, sex matched thyroid cancer patients who had not exposed to $^{131}$I as controls [14]. They reported the risk as standardized incidence ratio (SIR) and calculated the same as the ratio between observed and expected numbers of cancers. When patients treated to ablate thyroid remnants were studied separately among those receiving (50 mCi of $^{131}$I, no significant overall risk was observed as compared to SIR of 1.54 and 1.8, in 50-100 mCi group and (100 mCi group, respectively. In a weighted regression analysis of overall SIRs the trend was statistically significant (p < 0.05). The authors concluded that the lesser the administered activity to ablate the remnant, lesser is the risk of second malignancy after $^{131}$I treatment.

The philosophy of large dose $^{131}$I ablation of remnant tissue is based on a contentious issue of "large dose not only ablate remnant but also ablate possible micrometastatic deposits". The proponents of initial high dose radioiodine ablation argue that low doses were less effective to ablate the micrometastases not visualized in post-therapy whole body scan and thereby will lead to higher recurrence rate, local as well as distant. However, this issue is already addressed by Mazzaferri and Jhiang, who found no difference in long-term tumor recurrence rate (7% Vs 9%) between low dose (29 - 50 mCi) and high dose (51 - 200 mCi) $^{131}$I remnant ablation groups [15]. The indication for thyroid remnant ablation will remain in dispute, until such issue is settled by a prospective randomized case-control study and the beneficial effect of $^{131}$I remnant ablation is proven beyond doubt, the dose (50 mCi) we propose, has the merit of being safe and economical.

We conclude, increasing the empirical $^{131}$I initial dose beyond 50 mCi results in plateauing of dose-response curve and thus, conventional high dose remnant ablation needs critical evaluation. Secondly, based on dosimetry results one should aim to deliver about 30,000 cGy to thyroid remnant, as higher doses does not appear to yield a higher ablation rate.

**References**

5. Bal CS, Padhy AK, Jana S, Basu AK. Comparison of low and high dose $^{131}$I ablation of remnant in differentiated thyroid cancer patients. In: Rao RS, Deo MG, Sanghvi LD,


Radioiodine therapy for pediatric patients with thyroid cancer

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From 1986 to 1998 753 patients under 16 underwent therapy for thyroid carcinomas. Of them lung metastases were diagnosed in 108 (14.3%) cases. These patients were selected for radioiodine therapy. At the time of Chernobyl Power Plant Disaster the majority of them (88, 81.5%) were under 5 years old and the rest 18.5% were at the age of 5 to 12. Sex ratio was 1.2f/1m. Most of the patients had an extended disease. Neck lymph nodes were positive in 103 (95.4%) cases including 76 (70.4%) with bilateral involvement of lymph nodes (pNlb). In 86 patients tumor invasion of surrounding tissues was diagnosed (pT4). Of them multifocal thyroid lesions were diagnosed in 39 patients (pT4b). Tumor histology was as follows: papillary carcinomas - 104, follicular - 3 and medullary - 1 (Table 1).

Table 1. Patients data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Children (age under 15)</th>
<th>Teenagers * (age 15-16)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>618</td>
<td>135</td>
<td>753</td>
</tr>
<tr>
<td>Patients with lung metastases</td>
<td>97 (15.8%)</td>
<td>11 (8.1%)</td>
<td>108 (14.3%)</td>
</tr>
<tr>
<td>Patients' sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-males</td>
<td>43</td>
<td>6</td>
<td>49</td>
</tr>
<tr>
<td>-females</td>
<td>54</td>
<td>5</td>
<td>59</td>
</tr>
</tbody>
</table>

*Important note: All the patients were children at the time of Chernobyl disaster
Initially thyroid tumors and regional metastases were removed by thyroidectomy with simultaneous unilateral or bilateral radical neck dissection. In 22 patients lung metastases were detected before surgery by routine X-ray and in 77 metastatic disease diagnosed after surgery by using radioactive iodine-131 uptake test. The number of radioiodine therapy courses ranged from 1 to 14. Delivered iodine-131 activity varied from 1.25 up to 43.7 Gbk. Response was received in 107 patients. There were 79 complete responders. In 28 patients a partial response or stabilization was reached. In this group the patients continue therapy. Tumor progression was in only one patient with medullary carcinoma after three courses of radioiodine therapy. All the patients are alive from 6 to 56 months after surgery (Table 2).

Table 2. The results of therapy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Children (age under 15)</th>
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<th>Total</th>
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<td>Overall information</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>74</td>
<td>5</td>
<td>79</td>
</tr>
<tr>
<td>Stabilization or partial response</td>
<td>22</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Cancer progression</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Duration of follow up for complete responders

<table>
<thead>
<tr>
<th>Duration</th>
<th>Children (age under 15)</th>
<th>Teenagers (age 15-16)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 12 months</td>
<td>13</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>12-24 months</td>
<td>34</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>24-36 months</td>
<td>20</td>
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<td>36-48 months</td>
<td>6</td>
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<td>6</td>
</tr>
<tr>
<td>48-60 months</td>
<td>1</td>
<td>0</td>
<td>1</td>
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</table>

Number of courses and response

<table>
<thead>
<tr>
<th>Effect</th>
<th>Number of courses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1  2  3  4  5  6  7  8  9  10 11 12 13 14 Σ</td>
</tr>
<tr>
<td>Complete response</td>
<td>1  4 16 12 10 13 8 5 3 3 1 0 2 1 79</td>
</tr>
<tr>
<td>Stabilization or partial response</td>
<td>2  5 4 6 5 1 3 1 0 1 0 0 0 0 28</td>
</tr>
<tr>
<td>Cancer progression</td>
<td>0  0 1 0 0 0 0 0 0 0 0 0 0 0 108</td>
</tr>
</tbody>
</table>
A complex evaluation of the efficiency of 131 I - Ablation in patients with differentiated thyroid carcinoma after surgery

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The efficiency of the thyroid ablation with 131-I in patients with thyroid carcinoma determines the prognosis and the following treatment. A total of 155 patients with differentiated thyroid carcinoma were operated during the period 1978-1994 (120 women and 35 men, aged 15 - 86 years), divided in 3 groups, according to the histological findings: follicular - 63 patients, papillar - 64 and mixed carcinoma - 28. All patients were followed 3 years after ablation, done with 30-100 mCi 131-I.

The following investigations were undertaken:
1. 131-I - uptake test. The corresponding values of 2, 4 and 24 hours in patients without a residual parenchyma were 1.1%, 0.6%, 0.3% and in those with residual parenchyma 1.5%, 3% and 12%.
2. Gamma camera scintigraphy after surgery for an evaluation of the residual thyroid parenchyma and metastases (fig. 1, fig. 2).
3. Determination the level of thyroglobulin (Tg), using immunoradiometric method (“Sorin-biomedica”, normal value 8.1 ng/ml).

Our results show (table 1) that in patients with a total ablation, Tg level was normal, while in those with metastases and recurrences it was above normal. The higher levels of Tg were found in patients with a follicular carcinoma, less high in those with mixed form and the lowest in the papillar carcinoma. In patients with recurrences, Tg was as high as 236 ng/ml, in those with lung metastases - till 1010 ng/ml and in bone metastases - till 1163 ng/ml.

As a conclusion we consider that the complex evaluation of the efficiency of 131-I treatment, using 131-I - uptake test, whole body scintigraphy and the level of thyroglobulin is a very informative and useful method for the state and the prognosis of the patients, treated with 131-I.

Table 1. Level of Tg in the serum of patients with 131-I - ablation of the thyroid after surgery.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Histological findings of thyroid carcinoma</th>
<th>Total</th>
<th></th>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follicular</td>
<td>Papillar</td>
<td>Mixed</td>
<td>N</td>
<td>X</td>
<td>N</td>
</tr>
<tr>
<td>with metastases and recurrences</td>
<td>14</td>
<td>542.6</td>
<td>11</td>
<td>309.7</td>
<td>4</td>
<td>314.2</td>
</tr>
<tr>
<td>without metastases and recurrences</td>
<td>49</td>
<td>7.6</td>
<td>53</td>
<td>7.8</td>
<td>24</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>63</strong></td>
<td><strong>64</strong></td>
<td><strong>28</strong></td>
<td><strong>155</strong></td>
<td></td>
<td><strong>110.0</strong></td>
</tr>
</tbody>
</table>
Fig. 1. Scintigraphy of the lungs with 131-I - metastases of thyroid carcinoma.

Fig. 2. Bone metastases in both femurs with pathological fracture on the right side.
Effectivity of iodine-131 for ablating metastatic lesions in differentiated thyroid carcinoma

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The role and contribution of radioactive iodine therapy in the treatment of thyroid cancer remain controversial. The purpose of this study was to determine the efficacy of I-131 therapy in ablating functioning metastatic lesions from well-differentiated thyroid carcinoma. Clinical variables associated with ablation of metastases were also identified.

Materials and Methods

We reviewed records of patients from 1991 to 1998 who had whole body I-131 scans done before and after high-dose (3.7 to 7.4 GBq, 100 to 200 mCi) I-131 therapy after thyroidectomy. Excluded from the study were those up Hurthle cell, medullary, anaplastic or poorly-differentiated histology, or when I-131 scan films were not available.

All patients presented with a nodular goiter and subsequently underwent total or near-total thyroidectomy. Patients who had subtotal thyroidectomy only or who had large remnants demonstrated on subsequent thyroid scanning underwent completion thyroidectomy. In three subjects metastasectomy was performed for well-circumscribed soft-tissue lesions.

Whole body scanning using 74 to 185 MBq of I-131 was performed at least one month after surgery. Thyroid hormone was withheld in all cases prior to scanning. Patients with demonstrable functioning remnants and metastases were given between 3.7 and 7.4 GBq of I-131 orally within months after surgery and at least a month after I-131 scanning. Whole body scanning was performed between three and eight days after therapy in patients who had who had ill defined lesions on the previous body scan but had elevated serum thyroglobulin levels. Thyroid hormone therapy was then instituted using 100 to 200 mcg/day of L-thyroxine.

Between four and 10 months after radioiodine treatment whole body scanning was repeated. For four to six weeks prior to scanning L-thyroxine was withdrawn. When necessary 25 mcg/day of liothyronine was substituted but withheld for at least three weeks before scintigraphy. Radioiodine therapy was given again when the scan still showed functioning remnants or metastases. Administered activity was equal to or higher than that given in the initial therapy but in no case was less than 5.6 GBq.

For this study, lesion ablation was defined as disappearance of focal tracer accumulation on subsequent whole body I-131. When lesions were equivocal the subsequent post-therapy whole body scan was used in correlation with serum thyroglobulin assay.

Continuous data were expressed as means and ranges. Chi-square test and t-test were use to analyze the association of clinical variables with success of ablation therapy.

Results

Eighty-seven patients (18 males and 69 females) with a mean age of 47.2 years (range 24-77 years) satisfied the inclusion criteria. There were 43 patients with papillary carcinoma, 38 patients with follicular carcinoma, and six patients with mixed histology. In the 87 subjects, 121 metastatic lesions were identified during the initial whole body scan after surgery.
Metastatic lesions were most commonly seen in the lymph nodes (n=54) followed by the bones (n=42), lungs (n=19), liver (n=4) and mediastinum (n=2).

Of the 121 metastatic lesions, 40 (33%) were ablated as of the last follow up. Lymph node metastases showed the highest ablation rate of 30% (27/54), followed by lung metastases with 26% (5/19) and bone metastases with 19% (8/42). One of two mediastinal lesions were ablated while none of the four liver metastases responded to therapy. Median cumulative administered I-131 activities before ablation was achieved for the three most common metastatic regions (lymph node, lung, bone) were 5.5 GBq (150 mCi), 11 GBq (300 mCi) and 18.5 GBq (500 mCi) respectively.

Complete ablation of all functioning lesions was achieved in 30 of the 87 patients (34%). Twenty-six of these 30 patients (87%) had only one metastatic lesion initially, and of these all except two lesions were in the lymph nodes.

The subjects showing complete ablation were significantly younger than those with incomplete ablation (mean age 43 years vs. 49 years, p = 0.04). Also there was a progressive decline in the success rate for complete ablation with advancing age (31%, 29%, 21% and 11% for ages >30, >40, >50 and >60 years respectively).

Patients with follicular carcinoma were less likely to respond completely to radioiodine therapy than those with papillary or mixed histology, (24% vs. 43%, p = 0.014) This is probably linked to the finding that follicular carcinomas had a relatively higher proportion of bone metastases while papillary carcinomas had a relatively higher proportion of the more responsive lymph node metastases.

It was observed that males had a lower complete response rate compared to females (17% vs. 39%, p = 0.0004). This is likely related to poorer follow-up since males underwent less radioiodine therapy sessions (mean of 1.6 sessions/patient) than females (mean of 2.6 sessions/patient) for those with unresponsive lesions.

At least three patients had progressive disease (one with follicular carcinoma developing anaplastic transformation) despite radioiodine therapy, and these died during the study period.

A comparison group of 205 consecutive patients showing functioning thyroid remnants localized to the thyroid beds, who received radioiodine ablation therapy, and who had post-radioiodine therapy I-131 scans was also analyzed. These patients usually received 3.7 GBq of I-131 (range 2.5 to 5 GBq). The ablation rate after the initial therapy was 94% and the remaining 6% responded completely after a second course of I-131 therapy.

Conclusion

This study demonstrated the low ablation rate (33% of functioning metastatic lesions complete ablation achieved in 34% of patients) obtained after high-dose I-131 therapy for patients with metastatic differentiated thyroid cancer. Repeated radioiodine therapy was necessary in the majority of cases.

Lymph node metastases, particularly if solitary, were the most likely to respond completely. Of the common metastatic sites the bones showed the lowest ablation rate and required the highest I-131 cumulative activity before response was demonstrated. Because of the metastatic distribution pattern, follicular carcinoma had a poorer response. Advancing age and the male gender were also associated with decreased ablation rates. Of the clinical variables, age appeared to be the only independent predictor of reduced response to I-131.

Because of the poor response of metastases to I-131, the value of performing radioiodine therapy while lesions are still localized needs to be further studied.
Comparison of Tc-99m Tetrofosmin and I-131 whole body scintigraphy for follow-up of well-differentiated thyroid carcinoma after I-131 therapy

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This study was conducted to determine the feasibility of using Tc-99m Tetrofosmin while under thyroid hormone therapy for demonstrating functioning thyroid tissue in patients who have received I-131 treatment for well-differentiated thyroid carcinoma. The images obtained were compared with conventional whole body I-131 scanning performed with the patient in the hypothyroid state.

Materials and Methods

Patients who have undergone total or near-total thyroidectomy for well-differentiated thyroid cancer and who subsequently received I-131 therapy were enrolled in the study. Iodine-131 activity ranging from 3.7 to 7.4 GBq have been administered to the subjects at varying intervals after surgery. L-thyroxine at a dose of 100-200 mcg/day was prescribed for those patients to whom radiodine treatment was not given soon after surgery. Between three and nine months after radioactive iodine therapy each patient underwent two whole body scanning procedures, once using I-131 while off thyroid hormone and a second imaging procedure using Tc-99m Tetrofosmin while receiving thyroid hormone therapy.

Iodine-131 scintigraphy was performed at least four weeks after discontinuing L-thyroxine therapy. Two patients received 25 mcg/day of liothyronine until three weeks before the scans were performed. Serum TSH in all of the subjects ranged from 38 to 120 mIU/L at the time of scanning. Imaging was performed using wide field of view gamma cameras fitted with high-energy collimators. Images were acquired one and two days after a 74 to 111 MBq oral dose of I-131 using 256 x 1024 matrices, byte mode with scanning speeds ranging from 8 to 15 cms/minute. Static images of the neck and chest were also obtained during the first scanning day for 10 minutes using a 256 x 256 x 16 matrix. Except in four patients, I-131 scanning was performed prior to Tetrofosmin imaging.

Tc-99m Tetrofosmin scans were obtained while the subjects have been taking L-thyroxine 100-200 mcg/day for at least a month. Imaging was initiated 10 minutes after injection of 740 MBq of the radiopharmaceutical aspirated from a multidose vial (Amersham). Anterior and posterior whole body scans were acquired using 256 x 1024 matrices, byte mode with scanning speeds ranging from 10 to 20 cms/minute. A 500,000 count planar image of the head, neck and chest was also obtained (256 x 256 x 16 matrix) immediately after the whole body scan. A wide field of view gamma camera with a low energy high-resolution collimator was used in all patients. The I-131 and Tc-99m Tetrofosmin scans were performed no more than three months apart.

Functioning residuals and metastases were identified. Relative accumulation of the radiopharmaceuticals or lesion contrast was graded semiquantitatively as follows: 0 - no uptake or equal to background; 1 - definite lesion, higher than background but borders not well-defined; 2 - lesion borders are well-defined but uptake is less than normal thyroid tissue; 3 - tracer uptake similar to or higher than normal thyroid tissue.
**Results**

Twenty-two lesions were identified in 11 patients (1 male and 10 females, ages 24-77 years). Six of the patients had papillary carcinoma, four had follicular carcinoma while one had mixed histology. Serum thyroglobulin measurements were available in nine of these patients, values ranging from 35 to 553 ng/ml. Seven of the lesions represented residual gland tissue in the thyroid fossae while the rest consisted of metastases to the cervical lymph nodes (n = 4), sternum (n = 3), lungs (n = 4), mediastinum (n = 2), skull (n = 1), pelvis (n = 1).

Twenty of the 22 lesions were detectable in both the I-131 and Tc-99m scans, for a positive concordance rate of 91%. In the other two lesions one in the thyroid fossa demonstrated accumulation of I-131 but not Tc-99m Tetrofosmin, while another patient showed Tc-99m Tetrofosmin uptake but not I-131 in a sternal lesion. Lesion contrast using I-131 however was generally better (Table 1). Using the semiquantitative scheme 11 lesions had higher uptake using I-131, and in six of these 11 the tracer uptake was two grades higher than when using Tc-99m. Seven lesions had equal uptake in both radiopharmaceuticals while in only four of 22 lesions was the Tc-99m Tetrofosmin uptake better than I-131.

The static planar images using Tc-99m Tetrofosmin were equal or superior to whole body scans for lesion identification, however the opposite was true for I-131. In this limited patient series, the substantial abdominal accumulation of Tc-99m Tetrofosmin did not interfere with lesion identification. Because of better counting statistics and a more appropriate gamma ray energy, some of the lesions appear better delineated with Tc-99m Tetrofosmin than with I-131.

**Table 1. Grading of lesion tracer uptake.**

*Comparison between Tc-99m Tetrofosmin and Iodine-131*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Iodine-131</th>
<th>Tc-99m Tetrofosmin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8*</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

* in eight patients without demonstrable tumor

For comparison another group of eight patients (three with papillary carcinoma, five with follicular carcinoma and one with mixed histology) with thyroglobulin levels ranging from 0.2 to 3 ng/ml and with no clinical evidence of tumor were also studied. In all of these patients I-131 and Tc-99m Tetrofosmin failed to demonstrate any functioning thyroid tissue. For lesion detection without regard to degree of uptake, the agreement beyond chance or kappa statistic between the two tracers was excellent with a value of 0.84.

**Conclusion**

Results of the study showed that Tc-99m Tetrofosmin is potentially useful as an imaging agent for detecting functioning residuals and metastases after I-131 therapy of well-differentiated thyroid cancer. Although image quality was generally better with the more tissue-specific I-131, concordance rate for lesion identification was very high. The radiopharmaceutical was able to demonstrate functioning thyroid tissue while the patient was under L-thyroxine therapy, thus avoiding the inconvenience, discomfort and possible growth of tumor cells associated with stopping thyroid hormone intake prior to I-131 scanning.
Differentiated thyroid carcinoma: Retrospective analysis of 50 patients with 5 years follow-up

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Introduction

The study aim was to evaluate the outcome on a sample of patients with differentiated thyroid carcinoma and a minimal 5 years follow-up.

Subjects and methods

The clinical records of all patients (pts) with thyroid carcinoma who had their primary treatment at our medical centre - IPOFG - in the year of 1990 were retrospectively reviewed. From a total of 69 pts, 19 were excluded (8 with non differentiated thyroid carcinoma and 11 were lost to follow-up).

From the fifty pts, 43 (86%) female and 7 (14%) male, with differentiated thyroid carcinoma and a minimal follow-up of 5 years were analysed (mean: 87 months). The age at diagnosis ranges from 11 to 87 years (average: 45 yr.; mean: 42.5 yr.). Histologically, 47/50 (94%) cases of papillary carcinoma (in 8 with follicular variant) and 3/50 (6%) follicular were found.

At the time of initial examination, 31 (62%) cases showed a single thyroid nodule, 8 (16%) cervical lymph nodes, 6 (12%) single thyroid nodule + cervical lymph nodes, 4 (8%) multinodular goiter and 1 (2%) multinodular goiter + cervical lymph nodes.

Therapeutic approach

All patients studied had undergone a thyroid surgical procedure: 43 (86%) total thyroidectomy and 7 (14%) unilateral lobectomy. Of these pts, permanent parathyroprival hypocalcemia (> 6 months substitutive therapy) occurred in 14 (28%) cases. Radioiodine was administered postoperatively to 37 (74%) pts, with a mean time interval of 3.3 months. From the total of pts treated with radioiodine, 3/37 (8.1%) had clinical registration of acute complications (nausea, xerostomia and diarrhoea).

Clinical outcome

From the total of 50 pts, 36 had no postoperative events. Fourteen showed metastization in the course of the disease: 6 cases were diagnosed when first radioiodine was performed (one pt remain with evidence of disease), in 7 cases new lesions were diagnosed during the course of the disease (2 pts remain with evidence of disease), and in one case a cervical recurrence occurred and patient died - Fig. 1.

In 13 cases metastases were shown: cervical lymph nodes in 8 cases, bone metastasis in 1 case, cervical lymph nodes + brain + lung metastases in 1 case, cervical lymph nodes + lung metastases in 2 cases and lung metastases in 1 case.
Conclusion

In the studied population, with a mean follow-up interval of 88.5 months, 92% (46) pts were in remission, 6% (3) were with evidence of disease and one pt died due to thyroid carcinoma.

**Fig. 1.**

**References**

Ablation rate in 410 pts with differentiated thyroid cancer


Ankara University Medical School, Nuclear Medicine Department. Ankara TURKEY

This study covers the results of radioactive iodine treatment given to 410 (306 female and 104 male, mean age 45.4 ± 8.9 yr.) pts operated for differentiated thyroid cancer in the period of 1985-1996. Mean follow up period was 5.4 ± 1.2 yr. All the pts had residual thyroid tissue lower than 10 gr. TSH was above 30 IU/ml. The doses following the first one were either the same or 30-50% higher than the previous one. The pts were grouped in three dose levels and % success was calculated for each group. None of the pts in group I had metastases before the I-131 treatment, 9/303 had metastases and all the pts in group III had metastases.

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th></th>
<th>Group II</th>
<th></th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>First dose</td>
<td>11</td>
<td>42.3</td>
<td>247</td>
<td>81.5</td>
<td>60</td>
</tr>
<tr>
<td>Second dose</td>
<td>14</td>
<td>53.9</td>
<td>45</td>
<td>14.8</td>
<td>13</td>
</tr>
<tr>
<td>Third dose</td>
<td>1</td>
<td>3.8</td>
<td>5</td>
<td>1.7</td>
<td>5</td>
</tr>
<tr>
<td>Fourth dose</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>1.7</td>
<td>2</td>
</tr>
<tr>
<td>Fifth dose</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Total # of pts</td>
<td>26</td>
<td>100</td>
<td>303</td>
<td>100</td>
<td>81</td>
</tr>
</tbody>
</table>

With the first treatments % success was 42.3 in group I, 81.5 in group II and 74.1 in group III. A total of 96.2 in group I, 96.3 in group II and 90.2 in group III was achieved after the second dose.

It is concluded that giving a standard dose of 75-125 mCi radioactive iodine must be the method of choice for treatment of differentiated thyroid cancer.
Results of treatment with $^{131}$I in the group of 1054 patients with differentiated carcinoma of thyroid

Prim. Dr SLOBODAN TASIC
Department of Nuclear Medicine, Institut for Oncology and Radiology of Serbia, Belgrade, YUGOSLAVIA

In Institute for Oncology and Radiology of Serbia, 699 patients of average age of 42 years, suffering from papillary (PTC) as well as 355 of average age of 46 years with follicular thyroid carcinoma (FTC), followed up 8 y. (SD) 1 - 34 years and (SD) 1 - 43 y. respectively, have been studied.

Fifty out of 1054 patients were children and adolescents (4.6%) of both sexes average of 16.6 y. (range: 5 to 20): 37/50 suffering from papillary carcinoma (girls 30/37 and 7/37 boys). In out of 50, follicular carcinoma was diagnosed (9/13 girls, 4/13 boys).

Distant metastasis were found in 36 (5.15%) PTC patients and 52 (14.65%) FTC patients. FTC - PTC relationship 1.44 : 1 and W - M relationship 1.93 : 1. Distant metastasis mostly appeared in the lung (61.33%), then in bone (33.96%), brain (3.77%) and liver (0.97%). In 34/1054 patients (12 PTC and 22 FTC), the distant metastases is proved at initial treatment of TC (3.23%). In our group of patients 4.75% develop distant metastases during the course of their disease.

Patients with distant metastases were in T4 stage (5/18) or in T3 stage (5/18) PTC and in T4 stage (6/35) or in T3 stage (6/35) FTC.

$^{131}$I uptake by metastasis disease were found in 24 PTC patients and 35 FTC patients.

<table>
<thead>
<tr>
<th></th>
<th>$^{131}$I Uptake by metastatic disease</th>
<th>Metastatic disease unable to trap $^{131}$I</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LUNG + BONE</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LUNG</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>BONE</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>BRAIN</td>
<td>/</td>
<td>1</td>
</tr>
<tr>
<td>LIVER + LUNG</td>
<td>/</td>
<td>1</td>
</tr>
<tr>
<td>LUNG UNILATERAL</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LUNG</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>BONE</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>BRAIN + LUNG + BONE</td>
<td>1</td>
<td>/</td>
</tr>
<tr>
<td>LIVER + LUNG + BONE</td>
<td>/</td>
<td>1</td>
</tr>
<tr>
<td>LUNG + BONE</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>BRAIN</td>
<td>/</td>
<td>2</td>
</tr>
</tbody>
</table>

All of this patients have got $^{131}$I therapy (3.7 GBq) in one to six doses.
Results of treatment with radioactive Iodine:

- 24/36 pts. with distant metastasis of PTC are cured with $^{131}$I among them complete remission (CR) in 14 pts. (58%) - follow up 12.1 yrs. Partially remission (PR) in 7 pts. (29%).

- 35/52 pts. with distant metastasis of FTC are cured with $^{131}$I (CR in 13 pts. - 37%) - follow up median 7 yrs., PR in 14 pts. (40%).

In our group of 1054 DTC patients monitored since 1965 (88 patients with metastases - 8.35%) only 53 (5.02%) patients have died as a result of thyroid cancer (18 patients PTC and 35 patients FTC).

Radioiodine uptake by metastatic disease were found in 10/18 PTC and 19/35 FTC patient who died, but metastasis was unable to trap radioiodine in 8/18 PTC and 16/35 FTC patients.

Between mortality and distant metastases appearance, there is a very close relationship. Survival for whole followed up group was 3 years and nine months: in case of noniodophyle metastases only one year and six months, but when metastases are iodophyle the survival time is about six years.

Distant metastases were found in 9 children and adolescents and all of 9 are in lung (8/9 milliar bilateral form, 1/9 unilateral macronodular form). All metastases are able to trap $^{131}$I.

After radioiodine therapy, average follow up of 11 years. There have been no deaths in children group.

Conclusion

Age, sex, tumor size, local invasion, extend of surgery as well as clinical stage and distant metastases (iodophyl or not), are important prognostic parameter for differentiated...
thyroid carcinoma. $^{131}$I therapy gives benefit to survival of those patients with distant metastasis able to uptake iodine.

References

Invited Lecture IV
Tuesday 19 January 1999 : 14.00 - 14.30
The management of hyperthyroidism

POSHYACHINDA M.
Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

There are many clinical forms of hyperthyroidism, it is necessary to determine the specific cause of hyperthyroidism in order to direct the treatment strategy accordingly. The most common cause of hyperthyroidism is Graves' disease, an autoimmune disorder which is characterized by the presence of thyroid stimulating immunoglobulin that bind to and stimulate the thyrotropin receptor resulting in thyroid overactivity. Toxic nodular goitres, which is more common in iodine deficient region, are the next most common cause of hyperthyroidism which is due to autonomous hyperfunctioning thyroid nodules.

The therapeutic approaches to treat hyperthyroidism are 1) antithyroid drugs to block new hormones synthesis and release, 2) surgery and 3) radioiodine for ablation of thyroid tissue. All therapeutic modalities are effective but the latter two methods are relatively definitive means to achieve remission of hyperthyroidism.

Antithyroid drug therapy is the preferred treatment for all children with Graves' disease and patients with small goitres and short duration of disease. However a long term remission from antithyroid drug treatment is approximately 50%.

Surgery is appropriate treatment only for patients who has a very large goitre with symptoms of compression in the neck or in patients with a cold nodule on thyroid scan.

Currently radioiodine therapy is the most common therapy for Graves' disease. It is increasingly used as first-line therapy especially in elderly patients. It is the treatment of choice for patients with recurrent hyperthyroidism after antithyroid drug or surgical treatment. Radioiodine is also the preferred treatment for toxic nodular goitre. Radioiodine therapy is most effective, safe and low cost. However it may aggravated Graves' ophthalmopathy. The only disadvantage of this mode of treatment is high incidence of hypothyroidism. It is crucial that the patients should be annually follow-up posttreatment so that hypothyroidism can be detected early and treated.
Hyperthyroidism

Tuesday 19 January 1999 : 14.30 - 15.30
Thyroidal functional status after 131-radioiodine therapy for hyperthyroidism using ablative and non ablative doses

MARCELA RIVERA, PEDRO PINEDA, TERESA MASSARDO, HAROLD MICHELS EUROPE, RICARDO LILLO, VERONICA ARAYA, CLAUDIO LIBERMAN, PAULINA SIERRALTA
Endocrinology Section and Nuclear Medicine Centre. University of Chile Clinical Hospital, Santiago, CHILE

The optimal dose for an adequate therapeutic approach for hyperthyroidism (HT) is still controversial. Ablative doses (>15 mCi or 555 MBq of 131 Iodine) require maintained thyroidal hormonal replacement and clinical supervision. In our Institution doses had tended to be higher than 15 years ago, because we feel more secure with a complete functional ablation to avoid recidives, especially, in patients with some difficulties in delayed clinical control.

The main objective was to evaluate the current status of patients treated in our Institution using different doses approach and also to know eventual short and long term complications associated to radioiodine.

The hypothesis were:
1. Higher radioiodine doses are able to obtain a faster and more adequate correction of HT
2. Hypothyroidism is obtained in a shorter period with higher doses
3. There are less recidive proportion with ablative radioiodine doses

Material and method

Inclusion Criteria:
1. clinical and laboratory diagnosis of HT
2. non suppressed radioiodine uptake
3. post therapy follow-up ≥ 6 months

Exclusion Criteria:
1. nodular disease
2. pregnancy

Subjects:

We could obtain confiable data from 126/500 patients treated with radioiodine because of hyperthyroidism between January 1988 to December 1997 at our Institution, principally from our medical records. Mean age was 39.6 ± 13.4 years old (range 14-75) and they were 77.8% female.

The diagnosis of hyperthyroidism was based on:
- symptomatology and physical findings of HT (24.5% with ophtalmopathy)
- non suppressed 131 iodine uptake: 55.8 ± 18.1%; range 15-96% at 24 hours
- T3 > 200 ng/ml; T4 > 12.5 µg/dl; TSH < 0.1 µUI/ml

Prior therapy with propiltiouracil (PTU) was received in 90% of the cases (300-1200 mg/day). The group receiving higher radioiodine doses were treated significantly longer. Most continue with PTU 1 week after therapy.

Dose calculation:

It was based on clinical size of the gland and also in the amount of radioiodine uptake. No formula was applied.
Clinical Follow-up:

It was performed through analysis of medical record and also by phone interview, obtaining information related to control, medications, symptomatology and laboratory tests. Mean follow up was 31.8 ± 28.7 months (range 6-115 months).

Patients were grouped in three categories according to their radioiodine doses as seen in Table 1.

Table 1. Characteristics of the population and radioiodine doses

<table>
<thead>
<tr>
<th>dose (range) (mCi)</th>
<th>n (%)</th>
<th>male / female</th>
<th>age (y.o.)</th>
<th>follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 (3.3-9.9)</td>
<td>33 (26)</td>
<td>8 / 25</td>
<td>42 ± 12*</td>
<td>48 ± 40 #</td>
</tr>
<tr>
<td>10-14.9</td>
<td>31 (25)</td>
<td>6 / 25</td>
<td>41 ± 14</td>
<td>31 ± 24</td>
</tr>
<tr>
<td>&gt;15 (15-25.5)</td>
<td>62 (49)</td>
<td>14 / 48</td>
<td>37 ± 12*</td>
<td>23 ± 17#</td>
</tr>
</tbody>
</table>

*p: 0.056,  #p: 0.0001

Results

Thyroidal function at the end of follow up.

Patients were classified considering their functional status at the end of the follow-up according to the doses received in Figure 1. With all doses the percentage of obtained hypothyroidism was higher than the other status (p < 0.00005).

Fig. 1. Thyroidal status at the end of follow up

Figure 2 shows the length of the period to obtain euthyroidism or hypothyroidism with different radioiodine doses. It was significant difference between the period in reaching hypothyroidism with the doses < 10 mCi versus > 15 mCi (p : 0.003).

Associated features
1. One female patient with mild cervical edema by clinical finding 4 days after 20 mCi of radioiodine.
2. Two patients with worsening of their prior opthalmopathy 2 weeks after the therapy and other with new one 2 months after it (doses between 10-13 mCi) There were no patients with this complication in the group with therapy > 15 mCi.
3. No cancer or leukaemia were observed in the follow-up period
4. Requirement of a second radioiodine therapy was necessary in 11 patients, 82% of them with doses under 15 mCi, Table 2. One other patient persisted hyperthyroid and she continued with incomplete follow up.

![Graph showing mean time to reach "successful" therapy.](image)

**Fig. 2. Mean time to reach “successful” therapy.**

**Table 2. Second radioiodine doses**

<table>
<thead>
<tr>
<th>Initial doses</th>
<th>n</th>
<th>Activity 1º dose mCi (range)</th>
<th>Time to 2º dose months (range)</th>
<th>Activity 2º dose mCi (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15 mCi</td>
<td>9 / 64#</td>
<td>5.9 ± 2.2* (3.3-10)</td>
<td>8.2 ± 3.4 (3-11)</td>
<td>14.3 ± 6.1* (5-25)</td>
</tr>
<tr>
<td>&gt; 15 mCi</td>
<td>2 / 62#</td>
<td>20.0 ± 0 (20 both)</td>
<td>22 and 10</td>
<td>20 both</td>
</tr>
</tbody>
</table>

# p : 0.03  * p : 0.001

Other unexpected events were 2 deliveries after receiving radiotherapy, one patient received 25 mCi during her 10-12 week (she had a normal gynecological echography prior to the dose at 8 week of pregnancy). The other patient received 21 mCi one month prior to become pregnant. Both pregnancies and deliveries were without incidents and malformations.

**Conclusion**

At our Institution the use of ablative radioiodine doses for the treatment of hyperthyroidism is safe and there were not demonstrated more early or delayed complications than using lower doses. A second dose was less necessary when using initial ablative therapy.

**Bibliography**

Radioiodine therapy in hyperthyroidism

Emerita C. Andres-Barrenechea, M.D., FPCP, FPSNM
Veterans Memorial Medical Center, PHILIPPINES

The introduction of I-131 in 1946 for the treatment of hyperthyroidism marked a historic event. It ushered in the era of radionuclides in medicine and led to the birth of nuclear medicine. Today, I-131 has become one of the most commonly used agents for the treatment of hyperthyroidism.

Ninety percent (90%) of its effect is due to beta radiation and 10% is due to gamma radiation. The mechanism of action is production of radiation thyroiditis (3-10 days) and chronic gland atrophy (over a period of three years).

To achieve the necessary dosage levels, four considerations are needed: maximal amount of I-131 taken by the thyroid gland, size of tissue to be irradiated, effective half life of the isotope in the thyroid and relative sensitivity of the thyroid to I-131.

There are two kinds of dosing - The preferred dose where 160 µCi/gram of tissue is given (15-20 mCi) or the usual dose 80 µCi/gram - (2 to 15 mCi). In giving these dosages, four basic approaches are utilized and two major principles are applied.

However, the precision in the calculation of I-131 dose makes very little difference in the outcome in any individual patients. The inherent sensitivity of the thyroid to radiation seems to vary widely for unknown reasons.

The success in treatment is high with the incidence of cure as follows: 70-86% in single dose; 10-20% using 2 doses and less than 5% required 3 or more doses.

Adjunctive therapy in the forms of antithyroid drugs, beta blocker and steroids may be needed.

There are short and long term complications where hypothyroidism is the most important complication. Long term follow-up is advocated by FT4 and TSH determinations. There is an unknown risk of malignancy and genetic damage.

Finally, I-131 has been a choice of treatment for hyperthyroidism with some considerations in the USA, Europe and Asia. It is rapidly effective, predictable and inexpensive.

A ten-year study (1988-1998) was done at the Veterans Memorial Medical Center on radiiodine therapy for hyperthyroidism. A total of 162 patients were given I-131 and hence were included in the study. There was a predominantly female population of 81%, while males consisted only 19%. The most frequent age group were those of the third and fourth decade of life. Clinically, the most frequent manifestations were weight loss, palpitations and/or arrhythmia, profuse sweats, fine tremors, exopthalmus and muscle weakness. Almost all the patients underwent radioactive iodine uptake and scan as well as FT3, FT4 or serum TSH by radioimmuno assay.

Most of the patients were given options as to the choice of management. Excluded from the study were pregnant women, individuals below 18 years of age and those with large goiters.
The properly selected patients were given anti-thyroids for three to four weeks or longer, except for five percent (5%) who had allergic reactions to the drug, so that I-131 was immediately given. Beta blockers were also prescribed. Ten percent (10%) were given steroids for severe ophthalmopathy. The anti-thyroids were stopped three to five days prior to ablation of the thyroid gland and an iodine-free diet was also prescribed.

Doses for I-131 given ranged from 7mci to 12 mci. foremost considerations were size of the gland and degree of toxicity. A total of 102 patients (63%) received 10mci; 42 patients (26%) received 7mci; a group of 9 patients (5.5%) received 8mci and another group of 9 patients (5.5%) received 12mci. Post RAI course were uneventful except for minor complaints of sialitis and neck pain.

Success rate of treatment was 92%, wherein symptoms were abated and gradual shrinkage of the gland was achieved. There were five cases where symptoms were not relieved and shrinkage of gland was not fully attained. Also, there were seven (7) patients wherein anti-thyroid drugs were to be continued for four to six months in decreasing doses.

The most common long-term complication was hypothyroidism which occurred in 9.2% of the patients. As soon as this was recognized, thyroid hormone was given. Hence, there is a need for long term follow-up.

**Conclusions**

RAI is the treatment of choice in hyperthyroidism in properly selected subjects. Treatment must be individualized. There is need for 4000 - 5000 rads to destroy over active follicular cells. Complications such as local tenderness are short term, while hypothyroidism is the most common long term complication. No fear of radiation induced genetic damage, leukemia or thyroid cancer (40-year follow-up). Serum T4 is a better gauge than serum TSH becomes sensitive later. Precise calculation-make a little difference in the outcome in the individual person due to inherent sensitivity. Low dosing decrease incidence of hypothyroidism but decrease effectivity. If hypothyroidism persists after two months, it is likely to be persistent.
From 1974 to 1998, 723 patients with hyperthyroidism between the ages of 24 and 71 years were treated by I-131 at the Department of Nuclear Medicine, Bach Mai Hospital, Hanoi, Vietnam.

**Table 1. Age and sex of hyperthyroid patients**

<table>
<thead>
<tr>
<th>Sex</th>
<th>No. of patient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>94</td>
<td>13</td>
</tr>
<tr>
<td>Female</td>
<td>629</td>
<td>87</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>30-50</td>
<td>487</td>
<td>67</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>203</td>
<td>28</td>
</tr>
</tbody>
</table>

The patients were estimated with clinical examination, RIA and IRMA for thyroid related hormones, thyroid uptake test, thyroid ultrasound and scintigraphy, blood and urinal test.

**Table 2. Clinical characteristics of patients with hyperthyroidism**

<table>
<thead>
<tr>
<th>No of patient</th>
<th>Goiter (*)</th>
<th>Bulging eyes (**)</th>
<th>Heart disorders (***)</th>
<th>Digestion disorders (****)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>32</td>
<td>21</td>
<td>48</td>
<td>14</td>
</tr>
</tbody>
</table>

Note: (*) : Thyroid gland weight estimated was over 50 gm.

(**): May accompanied another ophthalmologic symptoms.

(***): ECG clearly changed and rapid pulses.

(****): Chronic diarrhea.

Formula for dose calculation: \( D = \frac{C \cdot W}{U} \)

Where

- \( D \) : The administered dose of I-131 (in mCi)
- \( U \) : The 24 hour thyroid uptake (%).
- \( W \) : Thyroid gland weight (in gm).
- \( C \) : Activity of I-131 destined into thyroid gland (from 80 to 120 μCi/gm [1, 2]).

**Table 3. The changes of clinical features after treatment by I-131**

<table>
<thead>
<tr>
<th></th>
<th>Increasing weight body</th>
<th>Reducing goiter size</th>
<th>Reducing bulging eyes</th>
<th>Reducing heart disorders</th>
<th>Disappearing digestion disorders</th>
<th>Reducing hands trembling</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>615</td>
<td>578</td>
<td>46</td>
<td>319</td>
<td>96</td>
<td>638</td>
</tr>
<tr>
<td>%</td>
<td>85</td>
<td>80</td>
<td>30</td>
<td>92</td>
<td>95</td>
<td>98</td>
</tr>
</tbody>
</table>

After treatment, there were any patient increasing bulging eyes.
Table 4. The change of the thyroid uptake and $T_3$, $T_4$, TSH concentrations in the hyperthyroid patients before and after treatment by I-131

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Thyroid uptake</th>
<th>$T_3$ (nmol/l)</th>
<th>$T_4$ (nmol/l)</th>
<th>TSH (mU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 h</td>
<td>24 h</td>
<td>2 h</td>
<td>24 h</td>
</tr>
<tr>
<td>Healthy adult</td>
<td>14.5 ± 3.0</td>
<td>32.5 ± 7.0</td>
<td>1.98 ± 0.54</td>
<td>109.17 ± 17.7</td>
</tr>
<tr>
<td>(n=50)</td>
<td></td>
<td>(n=50)</td>
<td>(n=80)</td>
<td>(n=80)</td>
</tr>
<tr>
<td>Hyperthyroidism (before I-131 therapy)</td>
<td>47.2 ± 15.9</td>
<td>70.9 ± 11.6</td>
<td>10.70 ± 6.72</td>
<td>282.12 ± 80.52</td>
</tr>
<tr>
<td>(n=130)</td>
<td></td>
<td>(n=130)</td>
<td>(n=98)</td>
<td>(n=56)</td>
</tr>
<tr>
<td>Hyperthyroidism (4-12 months after I-131 therapy)</td>
<td>15.9 ± 5.6</td>
<td>31.9 ± 6.4</td>
<td>1.79 ± 0.95</td>
<td>109.88 ± 43.10</td>
</tr>
<tr>
<td>(n=40)</td>
<td></td>
<td>(n=40)</td>
<td>(n=94)</td>
<td>(n=100)</td>
</tr>
<tr>
<td>Hyperthyroidism (4-10 years after I-131 therapy)</td>
<td>-</td>
<td>-</td>
<td>2.10 ± 0.48</td>
<td>110.21 ± 24.69</td>
</tr>
<tr>
<td>(n=49)</td>
<td></td>
<td></td>
<td>(n=49)</td>
<td>(n=45)</td>
</tr>
</tbody>
</table>

The general results of our patients are following:

- Euthyroid status (4 years after I-131 treatment) : 73.3%.
- Recurring hyperthyroidism : 20%
- Hypothyroid complication : After 4-12 months of treatment : 3%, after 4 years of treatment : 7.7 %, after 6 years of treatment : 14%.

So the cumulative hypothyroid rate is 2.5% per year.

The number of administrated doses are: One dose in 578 patients (80%), two doses in 109 patients (15%), three doses in 36 patients (5%).

The average time giving dose of all patients (k) is : 1.3

\[ k = \left[ \frac{(578 \times 1) + (109 \times 2) + (36 \times 3)}{723} \right] = 1.3 \]

In 723 hyperthyroid patients after treatment with I-131, there were no complication of thyroiditis, thyroid storm, laryngitis, genetic disorder and thyroid cancer. However, we observed an increase of erythrocyte number and hemoglobin value in the majority of treated patients. Formula of leukocytes was not changed in these patients [3, 4].

**Conclusion**

I-131 treatment is indeed effect for hyperthyroidism and is one of therapeutic methods, which should be selected. However, an education campaign to expand this method even in children is necessary in Vietnam.

**References**

Iodine -131 therapy for thyroid diseases -
Doses, new regulations and patient advices

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The therapeutic use of I-131 has been widely used in patient care over the past 50 years. Its main applications are in hyperthyroidism and functioning thyroid cancer both to ablate the remnant tissue or to burn metastasis. The indications, doses, regulations of its use, precautions and guidelines defer in different centers and countries. Due to these different criteria the Chilean Society of Endocrinology and Metabolism invited an expert panel to discuss the situation and to issue a consensus document with clinical recommendations and radiological protection advice (ref. Michaud P. “Proposición de concensos para el uso de 131I en el tratamiento de la tirotoxicosis y el cáncer del tiroides”. Rev Med Ch 1998;126:855-865).

Some of the proposals of the consensus committee are: 1. I-131 should be indicated in agreement by the endocrinologist and the nuclear medicine physician. 2. Pre-treatment I-131 thyroid uptake must be performed. 3. The only contraindications for treatment is pregnancy, in children it might be used with caution. 4. For thyrotoxicosis both a calculated or an ablative dose (555 MBq) criteria are acceptable In this case a secondary hypothyroidism must be considered an objective rather a complication. 5. In uninodular toxic goiter a 1110 MBq dose is recommended. 6. Iodine free diet should be restricted only for cancer patients. 7. Propylthiouracil (PTU) must be discontinued 5 days before treatment and it should be reinitiated 5 days latter. 8. The indication of prophylactic use of corticoids in patients with Graves’ disease still require more clinical data to support its use. 9. In case of treatment failure, the dose should not be repeated before six months of follow-up. 10. For cancer patients with intrathyroid disease an ablative dose of 3700 MBq should be administered 4 weeks after total thyroidectomy or with a TSH level above 30 μUI/ml. 11. A whole body scan should be done one week latter. 12. Follow-up whole body scan should be used only if there are clinical suspicion of metastasis. Thyroid hormone replacement must be discontinued for 30 days or with a TSH value above 30μUI/ml. A 185 MBq dose of I-131 is recommended for follow-up scan in order to ovoid thyroid tissue stunning. 13. For treatment of metastasis a dose of 5700 to 7400 MBq is recommended if there are cervical lymphatic nodes or distant metastasis.

Since there are not local regulations for patient releases after the administration of 131I we recommended to adopt the criteria proposed by the United States Nuclear Regulatory Commission (NRC) published as 10 CFR 35.75 and the Regulatory Guide 8.39, “Release of Patients Administered Radioactive Materials”. According to this regulation the physician in charge may authorize the release from its control any individual who has been administered radiopharmaceuticals or permanent implants containing radioactive materials if the total effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 5 millisieverts (0.5 rem). This proposal change a general limit to an individual based estimation of the radiation risk.

In this presentation a Patient Advice Guide is also presented to ovoid the unnecessary radiation to the general public, health worker and the environment.
Radiolabelled peptides: New radiopharmaceuticals for targeted therapy

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Preparation, quality control and animal test of $^{153}$Sm DTPA-Octreotide

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Somatostatin is a 14 amino acid containing peptide. The native hormone is susceptible to rapid enzymatic degradation, therefore, it is not suitable for long-term therapeutic use. For that reason, synthetic derivatives with a similar bioactive structure as somatostatin have been developed, which are not only less susceptible to biologic degradation but also have a strange inhibitory effect on hormone release by the relevant tumors. This peptide has a large biologic half-life than somatostatin itself and, hence, prolonged inhibitory effects on normal growth hormone production. Large number of high-affinity binding sites for native somatostatin and synthetic octreotide have been defected on most endocrine active tumors. But octreotide cannot be radiolabeled easily with a gamma-emitting radionuclide, a synthetic analogue (tyr$^3$-octreotide) has been developed in which phenylalanine has been replaced by tyrosine allowing radiiodination of the molecule. This compound has been used successfully as an iodine-123 radioligand for in vitro and in vivo somatostatin receptor studies. The procedure is now performed using $^{111}$In-DTPA-octreotide, a DTPA-coupled somatostatin analog, characterized by easy and efficient labeling, fast clearance and predominantly renal excretion, with only minimal hepatobiliary clearance. Furthermore, number of publications reporting on the use of other radioactive peptide for scintigraphic demonstration of various tumors and infectious processes. This work studied very litter of in this topic in China. But it is studied in labeling Tyr$^3$-octreotide with $^{131}$I ($^{123}$I), and labelling DTPA-octreotide with $^{111}$In, $^{99}$Tc$^m$ etc. Our research is to find the clinical agents for therapy of somatostatin receptor positive tumors. This report has done the research work of labelling DTPA-octreotide carrier-containing radionucides $^{153}$Sm.

**Materials and methods**

DTPA-octreotide were obtained from Peptide Int. Japan. DTPA-octreotide was labelled in different molar ratios of Samarium-153. The radiochemical purity of labelled peptide was checked by HPLC with a Waters 600E multisolvent delivery system connected to a μ-Bondapak-C18 reversed-phase column (300 mm x 4.0 mm, particle size 10 μm). Elution was carried out at a flow of 1 ml/min, with a linear gradient of 40% to 80% methanol in 0.05 mol/L acetate buffer solution in 20 min and latter composition was maintained for another 5 min. Eluted was monitored on-line (pH=5.5, sample volume: 10 μl, flow pool volume: 150 μl) using a radioisotope monitor (EG&G Berthold).

Animal test: A rat (weight 15-18 g) was injected 0.1 ml $^{153}$Sm-DTPA-octreotide (concentration: 0.1 mCi/ml) by tail vein. The rat was killed at different postinjection. Tissue distribution data showed that, I) Different molar ratios of $^{153}$Sm-DTPA-octreotide was similar rate of metabolism in rats. II) The labeling compounds was dissociated in vivo. III) The dissociation in vivo changed with the molar ratio of $^{153}$Sm-DTPA-octreotide IV) Low specific activity Samarium-153 labeled octreotide not a good idea for somatostatin receptor therapy.
Percent injected dose of $^{153}$Sm-DTPA-octreotide per gram of tissue sample (%ID ± SE, n=3)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>blood</th>
<th>liver</th>
<th>kidneys</th>
<th>lung</th>
<th>heart</th>
<th>spleen</th>
<th>adrenals</th>
<th>intestines</th>
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<tr>
<td>0.5 h</td>
<td>0.83</td>
<td>0.98</td>
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<td>0.39</td>
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<tr>
<td></td>
<td>1.02</td>
<td>2.05</td>
<td>4.52</td>
<td>0.12</td>
<td>0.62</td>
<td>0.74</td>
<td>0.95</td>
<td>0.41</td>
<td>0.39</td>
</tr>
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<td>1.45</td>
<td>8.05</td>
<td>0.44</td>
<td>0.21</td>
<td>0.13</td>
<td>2.13</td>
<td>0.65</td>
<td>0.17</td>
</tr>
<tr>
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<td>0.28</td>
<td>4.41</td>
<td>6.32</td>
<td>0.35</td>
<td>0.34</td>
<td>0.22</td>
<td>1.85</td>
<td>0.24</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>0.33</td>
<td>18.9</td>
<td>3.47</td>
<td>0.37</td>
<td>0.18</td>
<td>0.18</td>
<td>1.52</td>
<td>0.43</td>
<td>0.26</td>
</tr>
<tr>
<td>24 h</td>
<td>0.02</td>
<td>2.05</td>
<td>0.74</td>
<td>0.04</td>
<td>0.02</td>
<td>0.02</td>
<td>1.70</td>
<td>0.01</td>
<td>0.02</td>
</tr>
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<td>0.01</td>
<td>9.82</td>
<td>0.23</td>
<td>0.02</td>
<td>0.02</td>
<td>0.05</td>
<td>0.52</td>
<td>0.01</td>
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</tr>
</tbody>
</table>

References


Studies in rats on octreotide labelled with Ga-67: A potential radiopharmaceutical agent for the treatment of somatostatin receptor-positive tumors

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2Institute of Nuclear Medicine, University Hospital, Basel, SWITZERLAND

The paper presents the biodistribution and analysis of elimination mechanisms in rats with $^{67}$Ga-[DFO]-octreotide. The agent was primarily proposed as a radiopharmaceutical having a potential to localize somatostatin receptor-positive tumors using gamma scintigraphy [1]. However, $^{67}$Ga is also an attractive radionuclide for radiotherapy as it emits Auger and conversion electrons that deposit the radiation dose over a short range in tissues (the maximal range of 90-110 μm [2]). The physical half-life of $^{67}$Ga is 78 hrs and the decay mode by an internal conversion allows one to follow the fate of the radionuclide in vivo and to estimate dosimetry in individual patients. For labelling of octreotide with $^{67}$Ga, desferrioxamine B (DFO) coupled to octreotide via the succinyl linker has been shown to form a stable chelating agent for binding of $^{67}$Ga [1].

The radiopharmaceutical was prepared by adding 4 μl of 1 mM [DFO]-octreotide (in 0.1% acetic acid) to 100 μl of 0.1 M ammoniumacetate pH 5.6 together with 10 μl of Ga-67-(NO$_3$)$_3$ (2.14 GBq/ml in 0.04 M HCl). Molar concentration ratio of [DFO]-octreotide to no-carrier added Ga$^{3+}$ was 32.05. After 60 min incubation, 2 μl of this mixture was diluted 100 times to 20 mM ammonium acetate and analyzed by HPLC (on a C18 column and 20 mM ammonium acetate pH 4.5, gradient: 0-10 min 0% acetonitrile, 10-15 min 0-45% acetonitrile, 15-20 min 45% acetonitrile). Radiochemical purity, determined by HPLC, was over 99%. For biological experiments, the agent was diluted 10 times with saline.

Pharmacokinetics of $^{67}$Ga-[DFO]-octreotide was determined on male Wistar rats weighing 220-260 g after intravenous administration of the agent in a volume of 0.2 ml. At different times after administration (from 5 min to 48 hrs), a blood sample and selected organs and tissues were removed to determine the distribution profile of the radiopharmaceutical (Table 1). Radioactivity in blood and most organs decreased relatively rapidly with time, on the other hand the radioactivity-time decrease in the kidneys was very slow and a long-term retention of radioactivity in the kidney (about 6% of the administered dose) was found. The high radioactivity concentration in the adrenals is connected with a high somatostatin receptor density in the organ. The radioactivity determined in the bowels was mostly due to a partial elimination of $^{67}$Ga-[DFO]-octreotide and/or its metabolites by bile, as 8% of the administered dose was excreted by faeces. The agent was eliminated mostly by urine and the urinary elimination rate was relatively rapid. The analysis of renal elimination mechanisms by employing the perfused rat kidney in situ has shown that the agent is not only filtered in the glomeruli, but probably also partially secreted by the renal tubules as the renal clearance of free (non-protein bound) $^{67}$Ga-[DFO]-octreotide was somewhat higher than the glomerular filtration rate. The binding of $^{67}$Ga-[DFO]-octreotide to rat blood cells was negligible and about one third of the agent was bound to rat plasma proteins (determined by equilibrium dialysis at 37°C). The paper has presented a new view of the problems under study.
### Table 1. Distribution of $^{67}$Ga-octreotide in rats

<table>
<thead>
<tr>
<th></th>
<th>5 min</th>
<th>60 min</th>
<th>48 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per cent dose in the whole organ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>4.26 ± 0.47</td>
<td>1.83 ± 0.28</td>
<td>0.95 ± 0.13</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.20 ± 0.04</td>
<td>0.29 ± 0.05</td>
<td>0.23 ± 0.05</td>
</tr>
<tr>
<td>Kidney</td>
<td>11.86 ± 3.85</td>
<td>8.88 ± 1.52</td>
<td>6.17 ± 0.38</td>
</tr>
<tr>
<td>Lung</td>
<td>1.34 ± 0.31</td>
<td>0.37 ± 0.12</td>
<td>0.02 ± 0.01</td>
</tr>
<tr>
<td>Heart</td>
<td>0.34 ± 0.04</td>
<td>0.09 ± 0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.21 ± 0.04</td>
<td>0.06 ± 0.01</td>
<td>0.06 ± 0.01</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.38 ± 0.89</td>
<td>1.20 ± 0.48</td>
<td>0.26 ± 0.07</td>
</tr>
<tr>
<td>Small intestine</td>
<td>3.25 ± 1.12</td>
<td>2.25 ± 0.61</td>
<td>0.50 ± 0.02</td>
</tr>
<tr>
<td>Colon</td>
<td>1.16 ± 0.15</td>
<td>0.57 ± 0.21</td>
<td>1.42 ± 0.45</td>
</tr>
<tr>
<td>Testes</td>
<td>0.20 ± 0.05</td>
<td>0.13 ± 0.05</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.07 ± 0.01</td>
<td>0.03 ± 0.02</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Brain</td>
<td>0.08 ± 0.02</td>
<td>0.02 ± 0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Per cent dose per 1% body weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>2.44 ± 0.22</td>
<td>0.55 ± 0.05</td>
<td>0.01 ± 0.01</td>
</tr>
<tr>
<td>Liver</td>
<td>1.45 ± 0.14</td>
<td>0.63 ± 0.10</td>
<td>0.36 ± 0.04</td>
</tr>
<tr>
<td>Adrenals</td>
<td>7.05 ± 0.82</td>
<td>11.19 ± 2.79</td>
<td>8.21 ± 0.85</td>
</tr>
<tr>
<td>Kidney</td>
<td>19.10 ± 1.68</td>
<td>13.28 ± 2.43</td>
<td>10.93 ± 1.32</td>
</tr>
<tr>
<td>Lung</td>
<td>2.13 ± 0.29</td>
<td>0.61 ± 0.10</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>Heart</td>
<td>1.04 ± 0.09</td>
<td>0.29 ± 0.05</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>Skin</td>
<td>1.11 ± 0.01</td>
<td>0.43 ± 0.11</td>
<td>0.03 ± 0.03</td>
</tr>
<tr>
<td>Fat</td>
<td>0.76 ± 0.03</td>
<td>0.34 ± 0.25</td>
<td>0.18 ± 0.11</td>
</tr>
<tr>
<td>Bone</td>
<td>0.57 ± 0.04</td>
<td>0.30 ± 0.03</td>
<td>0.37 ± 0.04</td>
</tr>
</tbody>
</table>

The investigation was supported by the Grant Agency of the Charles University, grant No. 34/1998/B CH/FaF.

**References**

Preparation and quality control of $^{[131]}$I-MIBG

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The radioiodinated blocking agent $^{[131]}$I-MIBG (m-iodobenzylguanidine) has been one of the most successful of recent pharmaceuticals, and now it is a valuable radiopharmaceuticals for diagnosis and treatment of pheochromocytoma and neuroblastoma et al [1].

Published methods for $^{[131]}$I-MIBG labelling differ greatly. But any procedure for $^{131}$I labelling mlBG has to meet the following criteria: (1) the radiochemical yield should be close to 100%; (2) the labelling procedure should be fast and simple; (3) the method should lead to reproduceble results to make it suitable for routine production. Based on “MW2” method [2], our institute has established a simple procedure for routine preparing high quality $^{[131]}$I-MIBG. The “MW2” method is suitable for the high specific exchange radioiodination of mIBG. In this method exchange occurs in the solid-phase under the mildly acidic and oxidizing condition, using amine sulfate as a solid state transfer catalyst, but the overall radiochemical yield is low and obtain high radiochemical purity $^{[131]}$I-MIBG should be passage through anion-exchang column. In our method, these problems have been well solved.

The following procedures for the preparation $^{[131]}$I-MIBG were developed in our Institute.

1. mIBG. 1/2 sulfate solution 1 ml
   (2 mg/ml water)
2. (NH$_4$)$_2$SO$_4$ solution 2ml
   (15 mg/ml water)
3. $^{[131]}$I-NaI 3000 MBq

$^{[131]}$I-MIBG
injectable solution — Quality control — (store at 4°C)

<table>
<thead>
<tr>
<th>procedure</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>heat to dryness at 120°C</td>
</tr>
<tr>
<td>2</td>
<td>160°C 1 h</td>
</tr>
<tr>
<td>1</td>
<td>cool</td>
</tr>
<tr>
<td>2</td>
<td>Dissolve in</td>
</tr>
<tr>
<td>10 ml sterile acetate buffer</td>
<td></td>
</tr>
<tr>
<td>pH = 5.5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Benzyl alcohol to 1%</td>
</tr>
<tr>
<td>2</td>
<td>ascorbic acid to 0.1 mg/ml</td>
</tr>
<tr>
<td>3</td>
<td>Autoclave</td>
</tr>
<tr>
<td></td>
<td>glass reaction bottle</td>
</tr>
<tr>
<td></td>
<td>oil bath</td>
</tr>
<tr>
<td></td>
<td>White solid</td>
</tr>
</tbody>
</table>

The unlabelled mIBG. sulfate is synthesized by the procedure described by Wieland et al [3]. To verify that the products indeed mIBG, we have performed the following analysis: melting point, U.V., IR, NMR, mass spectroscopy and quantitative elemental analysis, the chemical purity of the product above 99%. The $^{[131]}$I-NaI solution is produced by dry process of our Institute with high quality and radioconcentration (up to 1 Ci/ml, carrier-free). The labelling procedure as above illustrate. In the procedure the glass reaction bottle was closed, the liquid in the reaction bottle drove out by heated at 120°C through a vent, and gathered in other bottle; the oxidizing condition was eliminated, and reagent masse, reaction time and temperature were inorder, high quality products would obtain with activity losses about 1-2%.

The radiochemical purity of the products were checked by ascending (Whatman No.1) paper chromatography developed for 10 cm in a jar containing a mixed developing solvent (n-butanol : glacial acetic : H$_2$O = 5 : 2 : 1). After developing, we found the free iodide near the origin (Rf : 0.2-0.3) $^{[131]}$I-MIBG migrated with solvent front (Rf : 0.9-1.0). In our experience, a typical run with this procedure give a radiochemical yield of $^{[131]}$I-MIBG of 98.5% with 1.5% free Ioine-131.
The deiodination of $^{[131]}\text{I}\text{mIBG}$ solution is very high without stabilizer at room temperature, due to the radiolysis. Add benzylalcohol to 1% as radical absorbers and bactericidal and ascorbic acid to 0.1 mg/ml as reductor, the deiodination only 2-3% when stored at room temperature after 5 days.

To date, $^{[131]}\text{I}\text{mIBG}$ injection has been prepared by this procedure in our Institute and used in several hospitals. Labelling efficiency have been consistently above 98%. Patients have been investigated with good clinical results, no reported untoward patient reactions.

In conclusion, the quantitative labelling yield up to 1500 MBq/mg (40 mCi/mg), the high radiochemical purity up to 98%, the reproducibility, simplicity and speed of the labelling procedure described above, prove this method fulfills the requirement for routine preparation of $^{131}$I labelled mIBG.

Reference

Meta (I-131) iodobenzylguanidine (MIBG): An analogue of the adrenergic neuron blocking guanethidine

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MIBG (meta. Iodobenzyl guanidine) can be considered as one of the most important ligands, bond to the neuroedrogen receptors in adrenal medulla. As a consequence of this specific interaction, all neuroendocrine tumors do also take up MIBG, giving opportunity for both diagnosis and therapy. Schematic diagram shows the synthesis of the non-radioactive MIBG using Donald & Weiland description followed by the radiolabelling technique using radionuclide I-131. Radioiodination is obtained from two different ligands: first from inactive MIBG (iodinated ligand) itself giving R.C. Yield of 90.9% in case of diagnostic dose and R.C. Yield of 64.4% in case of therapeutical dose. Second from inactive MIBrBG (bromonated ligand) giving R.C. Yield of 99.3% and R.C. yield of 89.5% respectively.

The influence of Na\(^{131}\)I specific activity is inversely proportional to the stability of the ready for injection \(^{131}\)I-MIBG. Accordingly it is observed that the specific activity of \(^{131}\)I-MIBG is decreased by 20% over a period of two weeks investigations, when therapeutical dose is used. Another side was focused on the reliability of the chromatographic system used. This system is simply based on using Thin layer chromatography (TLC).
The development of meta-iodobenzylguanidine analogues for the therapy of neuroendocrine and other tumors

G. Vaidyanathan and M. R. Zalutsky
Duke University Medical Center, Durham, North Carolina, USA

Meta-iodobenzylguanidine (MIBG) is an analogue of the neurotransmitter, norepinephrine (Fig. 1). Radioiodinated MIBG has been used extensively for the localization and therapy of neuroendocrine tumors such as neuroblastoma and pheochromocytoma. To improve the therapeutic usefulness of this approach, we developed a no-carrier added (n.c.a.) synthesis for MIBG, and several analogues with potential advantages.

![Chemical structures](image)

Fig. 1.

To date, radioiodinated MIBG used in clinical applications has been prepared by isotopic exchange (ex MIBG) and hence contains significant amount of unlabeled material (carrier). Since MIBG is taken up by target cells by a saturable active uptake-1 mechanism, it was hypothesized that it might be possible to improve its tumor localization through the use of a n.c.a. preparation. N.c.a. MIBG was prepared in more than 90% radiochemical yield from a silicon precursor under mild conditions [1]. In vitro studies using SK-N-SH human neuroblastoma cells showed that the uptake of n.c.a. [\(^{131}\)I]MIBG remained constant over a 2-3-log activity range, while that of ex [\(^{131}\)I]MIBG decreased more than 8-fold, demonstrating the saturability of uptake of [\(^{131}\)I]MIBG by SK-N-SH cells (Fig. 2). In normal mice, significantly higher uptake of n.c.a. [\(^{131}\)I]MIBG over ex [\(^{131}\)I]MIBG also was seen in innervated tissues such as heart and adrenals. Higher tumor-to-normal tissue ratios were obtained for n.c.a. [\(^{131}\)I]MIBG, compared to that for ex [\(^{131}\)I]MIBG, in athymic mice bearing SK-N-BE(2c) human neuroblastoma xenografts.

For the treatment of micrometastases, which are often associated with neuroblastoma, the long range \(\beta\)-particles of \(^{131}\)I may be suboptimal. The \(\alpha\)-particles of \(^{211}\)At on the other hand, have a range of only a few cell diameters and thus, could be ideally suited to maximizing fractional dose deposition in micrometastases. In addition, the \(\alpha\)-particles are high linear energy transfer radiation with a relative biological effectiveness greater than \(\beta\)-particles. To investigate this possibility, meta-\[^{211}\text{At} \text{astatobenzylguanidine}\] (\[^{211}\text{At}]\text{MABG}\) was prepared in excellent radiochemical yields. As shown in Table 1, the in vitro binding of \[^{211}\text{At}]\text{MABG}\) to SK-N-SH cells was similar to that of n.c.a. [\(^{131}\)I]MIBG. Like MIBG, the uptake of \[^{211}\text{At}]\text{MABG}\) was blocked by various uptake-1 blocking agents and conditions suggesting that
[211At]MABG is an excellent analogue of MIBG. The clonogenic potential of SK-N-SH cells following treatment with [211At]MABG, [211At]astatide and n.c.a. [131I]MIBG as a function of activity concentration gave a $D_0$ value of 5.8 nCi/ml for [211At]MABG, compared with 10,375 nCi/ml for [131I]MIBG, implying a more than 1,000-fold higher cytotoxicity for the α-particle emitting analogue. That the exquisite cytotoxicity of [211At]MABG is indeed due to its specific uptake and retention in SK-N-SH cells was demonstrated by the fact that the $D_0$ for [211At]astatide, 482 nCi/ml, was more than 80-fold higher than that for [211At]MABG.

Table 1. Uptake of n.c.a. [131I]MIBG, ex [131I]MIBG and [211At]MABG by SK-N-SH cells in vitro as a function of activity concentration.

<table>
<thead>
<tr>
<th>Log CPM</th>
<th>Specific uptake (percent of input)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.c.a. [131I]MIBG</td>
</tr>
<tr>
<td>4.0</td>
<td>48.9 ± 0.8</td>
</tr>
<tr>
<td>5.0</td>
<td>48.0 ± 1.1</td>
</tr>
<tr>
<td>5.4</td>
<td>47.3 ± 0.6</td>
</tr>
<tr>
<td>5.7</td>
<td>45.1 ± 1.2</td>
</tr>
<tr>
<td>6.0</td>
<td>43.5 ± 0.6</td>
</tr>
<tr>
<td>6.3</td>
<td>44.3 ± 2.8</td>
</tr>
</tbody>
</table>

For positron emission tomographic applications, a $^{18}$F-labeled analogue of MIBG, 4-$^{18}$F]fluoro-3-iodobenzylguanidine ($^{18}$F]FIBG), was developed. It will be ideal if the same molecule is amenable for labeling either with a positron emitter or with a therapeutic nuclide without changing the chemical properties. Since the pharmacokinetics/biodistribution of these two molecules are expected to be same, one could predict dosimetry from PET data obtained with the positron emitter-labeled agent for a therapy using the same molecule labeled with therapeutic nuclide. Towards this goal, we have developed a no-carrier-added synthesis of 4-fluoro-3-[131I]iodobenzylguanidine, [131I]FIBG (Fig. 1) from a silicon precursor [2].

When performed in a paired-label format, the specific binding of [131I]FIBG to SK-N-SH cells remained fairly constant (45-60%) over 2-3-log activity range and was 11-14% higher (p < 0.05) than that of [125I]MIBG. The uptake of [131I]FIBG and [125I]MIBG by this cell line was reduced by various uptake-1 blocking agents suggesting that uptake of [131I]FIBG by this cell line is specific and is mediated through an active uptake-1 mechanism. From a paired-label cell retention study using SK-N-SH cells, it was shown that about 70% of initially bound [131I]FIBG was retained at the end of 3 days. In comparison, this value for [125I]MIBG was about 25%. This suggests that, compared with [131I]MIBG, [131I]FIBG may deliver higher integrated dose to the tumor. Further studies are proceeding in cell culture and animal models to determine if these analogues show sufficient promise to warrant clinical evaluation.

References

Experience of radionuclide therapy with monoclonal antibodies and peptide

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Monoclonal antibodies to the pretargeting approach: Developments in radiopharmaceuticals for RIT

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Monoclonal Antibodies

Wednesday 20 January 1999 : 10.00 - 10.30
The preventive study of gastric cancer peritoneal micrometastasis in nude mice with $^{188}$Re-labeled monoclonal antibody 3H11

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In advanced gastric cancer, especially when the serosa is invaded, the plantation of cancer cells in peritoneal is common and it affects patients' survival time severely. On the basis of successfully labeled monoclonal antibody 3H11 with $^{188}$Re, we investigated the effect of RIT (Radio Immuno Therapy) with $^{188}$Re-3H11 on preventing the establishment of gastric cancer cells peritoneal micrometastasis in nude mice.

Method

1. $^{188}$Re Labeled Antibody

The direct method was employed with $^{188}$Re radiolabeled monoclonal antibody. The entire preparation was described in detail elsewhere [1].

2. RAIT in Nude Mice

After $1 \times 10^6$ BGC -823 gastric cancer cells were injected into the peritoneal cavity of each mouse., 40 BABL/C nude mice were divided into 8 groups. Each group received the various doses of $^{188}$Re-3H11 or $^{188}$Re-IgG or saline I.P. 16 hours post-operation. The injected volume of each mouse was 1.0 ml. The injected doses of each group were (A) saline, (B) 7.4 and (C) 37 MBq $^{188}$Re-IgG, (D) 7.4 MBq, (E) 18.5 MBq, (F) 37 MBq, (G) 55.5 MBq and 74 MBq $^{188}$Re-3H11 respectively.

Results

(1) The survival time depended on injected doses during 0 to 37 MBq. That of saline group, 7.4 MBq and 18.5 MBq, 37 MBq $^{188}$Re-3H11 group was $33.5 \pm 3.3$ days, $37.5 \pm 4.2$ days, $45.2 \pm 6.8$ days and $170 \pm 25.3$ days respectively. But when injected doses was 55.5 MBq and 74 MBq, the survival time was significantly reduced. The dead reason was internal hemorrhage after injection 18 days and intestinal liquefacent ulcer after injection 5 days respectively. (2) The mice hemogram were reduced to lowest after postinjection 14 days. But they recovered after 28 days. (3) The survival time of injected 74 MBq $^{188}$Re-3H11 group was more than 5 times than saline group and about 3 times of 74 MBq $^{188}$Re-IgG group ($p < 0.05$) (See Fig. 1).

Conclusion

During probably injected doses, early postoperative $^{188}$Re-3H11 I.P. is effective and safe in the prevention of intra-peritoneally injected gastric cancer cells from surviving, growing and disseminating in nude mice.
Fig. 1. Relation of the survival time to injected doses and pharmacy

Reference

A method to label MoAb with $^{153}$Sm-HETA using 1, 5, 9, 13-tetraazacyclohexadecane N,N',N″,N‴ tetraacetic acid (HETA) as a new bifunctional chelator was developed. HETA was synthesized in our laboratory by reaction between chloroacetic acid and ano-N4 ligand in aqueous solution at 0°C overnight followed by a precipitation at pH 2.0 and dried under vacuum (m.p. 242-244°C). The product was characterized by IR, RMN and thermogravimetric analyses showing high purity [1].

Samarium-153 chloride was obtained by neutron irradiation of 10 mg of enriched Sm$_2$O$_3$ ($^{152}$Sm, 99.4 %, from ISOTEC Inc.) in a Triga Mark III reactor at a flux in the central thimble of 3 x 10$^{13}$ n cm$^{-2}$ s$^{-1}$ for 20 h. [2] After irradiation 100 µL of 12 N chloride acid was added to the irradiation vial and stirred for 1 min followed by the addition of 900 µL of injectable water and also stirred for 2 min. The average radioactive concentration was 37 GBq/mL.

Sterile and apyrogenic V vials were prepared to contain 1.0 mg (2.17 x 10$^{-3}$ mmol/L) of HETA in 1.0 mL of 0.5 M bicarbonate buffer (pH 8.3) plus 20 µL of 2.5 N NaOH then 10 µL of SmCl$_3$ solution (4.9 x 10$^{-4}$ mmol/L Sm, 370 MBq) was added and the mixture, with a final pH 9.0, was incubated at 78°C for 3 h. Radiochemical purity was evaluated by TLC utilizing aluminum cellulose sheets (Merck) as the stationary phase with methanol : water : ammonium hydroxide (20 : 40 : 2) as the mobile phase. Sm$^{3+}$ remained at the origin (R$_f$ = 0) and $^{153}$Sm-HETA traveled with the solvent front with a R$_f$ value of 0.9-1.0.

Murine monoclonal antibody (MoAb) IgGl for cell against carcinoembryonic antigen (CEA) was supplied by the Center of Molecular Investigations (CIMAB, Havana, Cuba) into vials containing 5.0 mL of a sterile and apyrogenic neutral phosphate buffer saline (PBS) solution with an antibody concentration of 1.0 mg/mL. To 1.0 mL of MoAb solution was added 1.0 mL of $^{153}$Sm-HETA solution and the mixture was incubated at room temperature (18-20°C) until 24 h. Quality control of the labeled antibody was evaluated by size exclusion HPLC analysis employing a ProteinPak 125 SW gel filtration column (Waters), with photodiode array detector. 0.1 M phosphate pH 7.4 at a flow rate 1.5 mL/min was used as mobile phase. Under these conditions Sm$^{3+}$ was retained into the column and for MoAb and $^{153}$Sm-HETA the retention time was 4.5 min and 6.9 min respectively (Fig. 1). The radiochromatographic profile was determined by collecting samples (Waters fraction collector) of uniform volume (0.5 mL) for counting in a external NaI (Tl) detector (NML, Laboratories, Inc.).

Radiochromatographic profile showed that 10 min after incubation only 15.6% of the radioactivity was associated with the MoAb (Fig. 2A) and after 24 h it increased to 95% (Fig 2B). Under these conditions 0.628 mol and 3.5 mol of $^{153}$Sm-HETA were coupled to each mol of MoAb after 10 min and 24 h respectively. The formation of $^{153}$Sm-HETA labeled MoAb by a simple incubation of the antibody with the samarium complex, even when $^{153}$Sm-HETA was prepared as a stable complex, could be explained on the basis that one HETA carboxyl group does not participate in neutralizing the charge of the metal and it is available to react with the amino groups of the antibody.

The specific activity of the labeled antibody was 111 MBq/mg (3 mCi/mg). Sm-153(III) is commercially available with specific activities up to 318.2 GBq/mg (Oak Ridge National...
Laboratory). Therefore, under the conditions described above $^{153}$Sm-HETA labeled MoAb could be obtained with specific activity up to 1.14 GBq/mg (30.7 mCi/mg).

In order to establish the therapeutic possibilities for $^{153}$Sm-HETA labeled MoAb obtained in this study it will be necessary to perform studies in normal and tumor-bearing mice.

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**Fig. 1.** HPLC separation (UV detector) of MoAb (Tr=4.5 min) and $^{153}$Sm-HETA (Tr=6.9 min)

**Fig. 2.** Radiochromatographic profile obtained during the preparation of $^{153}$Sm-HETA labeled MoAb A) 10 min after incubation B) 24 h after incubation.

**References**

The binding assay of $^{153}$Sm-EDTMP in vivo and in vitro

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$^{153}$Sm-EDTMP has been used widely in the clinic as a successful therapeutical radiopharmaceutical for bone tumor and bone metastasis lesion [1]. In the post several years, we have tried to do some thorough research, such as, the radiation condition of the natural samarium ($^{152}$Sm, 26.7%) and enriched abundance samarium ($^{152}$Sm, 98.7%), the paper chromatogram of $^{153}$Sm-EDTMP preparation [2], the relation of the $^{153}$Sm-EDTMP stability and EDTMP/Sm molar ratio, the process quality control of the $^{153}$Sm-EDTMP labeling technique and the $^{153}$Sm-EDTMP stability interfered by the medium, pH and the total radiation dose [3], and so on. With the more and more clinic experiments, the behavior of the ligand and its coordination complex in the living things has been focused.

We planned several experiments for the action of the EDTMP and $^{153}$Sm-EDTMP with the high efficient waters ultrahydrogel™ 120 µm HPLC column (7.8 x 300 mm), (1) the in vitro competitive binding assay of the $^{153}$Sm-EDTMP, $^{153}$SmCl₃ and the cysteine, BSA, mouse plasma. (2) the urine and the extracting solution of the liver and kidney homogenate after the $^{153}$Sm-EDTMP $^{153}$SmCl₃ injection in mouse. (3) the HPLC analysis of the production radiation self decomposition with large dose.

HPLC analysis: the mobile phase 0.85M PBS (pH = 7.5), rate 0.5 ml/min, 15 µl, uv 230 nm and radio detect in line. The retention time of $^{153}$Sm-EDTMP, EDTMP is about 13 min. Our results is: (1) the $^{153}$SmCl₃ not only can bind with the cysteine, BSA and the mouse plasma in vitro (fig. 2), but also can bind with the liver protein in vivo. So the $^{153}$SmCl₃ should be limited as small as possible in the production solution. (2) $^{153}$Sm-EDTMP is not bind with the mouse plasma (fig. 2), the cysteine, BSA (fig. 1). $^{153}$Sm-EDTMP is not found in the extracted solution of the liver and kidney homogenate; $^{153}$Sm-EDTMP is not decomposed in the urine (fig. 3). So $^{153}$Sm-EDTMP is stable in vivo. (3) $^{153}$Sm-EDTMP radiation self decomposition is not detected with large dose in the term of validity though the color of solution has changed. But A small degradation peak has been found in the production solution in two months.

Fig. 1. The competitive binding assay HPLC of the $^{153}$SM-EDTMP and the cysteine, BSA
Fig. 2. The competitive binding assay of $^{153}\text{SmCl}_3$, $^{153}\text{Sm-EDTMP}$ with mouse plasma

Fig. 3. The 2 hours urine HPLC after $^{153}\text{SM-EDTMP}$ injection

References

Among the aminomethylene phosphonic acid complexes of samarium studied, $^{153}$Sm EDTMP complex has been proved to be a good therapeutic agent for the treatment of skeletal metastases [1,2]. We have synthesised a few more α-aminophosphonic acids to investigate their suitability for complexation with radiometals and the efficacy of these complexes as bone seeking agents. The present paper describes the complexation of $^{153}$Sm with propylene diamine tetra methylene phosphonic acid (PDTMP) and its biodistribution studies. The ligand was synthesized following a method described for the synthesis of EDTMP with modifications [3]. After ascertaining the purity of this ligand, it was used for complexation with $^{153}$Sm. Experimental parameters were varied to optimize and obtain quantitative complexation.

$^{153}$Sm was produced by irradiating 1 mg of enriched $^{152}$Sm as Sm$_2$O$_3$ at a flux of 2.2x10$^{13}$ n/cm$^2$/sec, for a week. Specific activities of > 500 mCi/mg were obtained. $^{153}$Sm-PDTMP complex was prepared by mixing a known quantify of the ligand solution in 2M NaOH with $^{153}$Sm as samarium chloride. The pH of the reaction mixture was adjusted around 12. The total reaction volume was kept about 1 mL. After reaction, the pH of the complex was adjusted to 7. The percentage complexation yield was estimated by paper chromatography in 0.9% saline on Whatman 3 chromatography paper. In this solvent, the $R_f$ of the complex was 1 and uncomplexed samarium remained at the point of spotting. The stability of the complex at room temperature (22°C) was studied by estimating the RC purity at different time interval. The in vitro bone mineral uptake studies were carried out at 37°C in serum environment. The biodistribution studies were also carried out on Wistar rats to study the bone uptake.

PDTMP complexed quantitatively with $^{153}$Sm at room temperature (22°C) in a reaction time of 2 hours. Optimum molar ratio was 1:66 (metal:ligand) and the optimum pH for complexation was 12. The complexation yield was poor below pH 12. A high ligand concentration was found necessary to inhibit the hydrolysis of Sm at this pH. The complexation yield was found to be less when the reaction was carried out at higher temperature (60°-80°C). Radiochemical purity of the complex as estimated by PC was found to be > 95%. The stability of the complex was found to be better when stored at pH 12 (Table 1). The in vitro bone mineral uptake studies which were carried out at pH 12 showed about 20% bone mineral uptake in 1 hour contact time with no deterioration of the complex at 37°C. The biodistribution studies carried out in Wistar rats showed ~30% of the injected dose in

![Chemical structure of PDTMP complexed with Sm](image-url)
bone at 24h p.i. Uptake in other organs, was insignificant except in liver which showed a slightly higher uptake. Work with other phosphonate ligands is in progress.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>pH 12</th>
<th>pH 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>98</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>98</td>
<td>88</td>
</tr>
<tr>
<td>24</td>
<td>98</td>
<td>88</td>
</tr>
<tr>
<td>48</td>
<td>97</td>
<td>87</td>
</tr>
</tbody>
</table>

Table 1. Radiochemical purity of $^{153}$Sm-PDTMP complex stored at 22°C

References


Influence of central metal ion on bone deposition of EDTMP chelates with different radionuclides

D. Pawlek, I. Woźniak, R. Mikolajczak, P. Garnuszek, I. Licinska

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2Drug Institute, Chelmska St. 30/34, 00-725 Warsaw, POLAND

Preparation, characteristic and comparative biodistribution study of the EDTMP chelates with different radionuclides i.e. Sm-153, Tc-99m, Cr-51, In-113m and Cu-64 have been described in this work. Aim of our study was an estimation of influence of central metal ion on EDTMP chelates stability both in vitro and in vivo, and bone deposition in healthy rats.

The EDTMP chelates of Sm-153, Cr-51, In-113m and Cu-64 were prepared by addition of 1 ml of each radioactive solution (1-5 mCi in 0.05 M hydrochloric acid) to the lyophilised sodium salt of EDTM (17.5 mg of pure acid), and then the reaction mixtures were mixed for 30 min at room temperature. 99mTc-EDTMP complex was prepared by tin(II) reduction of pertechnetate ion in the presence of chelating ligand and ascorbic acid (0.5 mg SnCb 0.8 mg ascorbic acid) EDTMP/ethylenediamine-tetrakis (methylene-phosphonic acid) was synthesised and prepared for labelling with radioisotopes according to the previously described procedure [1].

The yields of radionuclides incorporation into EDTMP chelates, in the function of pH and stoichiometry of reactions, were monitored by TLC using plastic sheets coated with cellulose and water-ethanol-monoethanolamine 10/5/0.015 v/v/v as the mobile phase. Paper electrophoresis method, in the four electrolytes i.e.: 0.1M acetate buff. pH 4.5; 0.1M natrium perchlorate pH 7.0; 0.1M borate buff 8.6 and 10.1, was used for characterization of the complexes and estimation of their stability in vitro.

The comparative biodistribution studies were done in healthy Wistar rats (male, weighing 190-250 g), 30 and 90 minutes post intravenous injection of 0.2 ml solution of each radioactive complex (radioactive concentration 1-2 mCi/ml, radiochemical purity greater than 98%).

The results of the EDTMP complexes formation with the radionuclides and their stable isotopes showed the dependence of reaction yield on the pH and stoichiometry. In most cases, ligand to metal ratio greater than 4, and pH of medium above 6 conducted to high complex yield (>98%). The yields of 153Sm-EDTMP and 113mIn-EDTMP formation were very high (98-99%) even at acidified solutions (pH 2.5-3).

Electrophoretic mobility of the complexes under the study was pH-depended, which was the result of dissociation of an uncoordinated phosphonic groups during the alkalisation of the analytical medium. At the pH 4.5, the single, slowly moving band to anode, were observed for each of the EDTMP chelates. Raising the pH of the electrolyte to 7 resulted in significant increase and differentiation of the complexes mobility. In contrary to the others, the single radioactive band of 99mTc-EDTMP complex showed at pH 4.5, with continuous raise of pH gave three main individuals with various mobility. These results suggest not only changes in protonation of the complex, but also the parallel creation of different type of 99mTc-EDTMP complexes.

The biodistribution study in rats resulted in differentiation of activity deposition in skeleton after intravenous application of the investigated complexes (Table 1). 90 minutes post injection, high activity uptakes in femur were observed for three EDTMP chelates i.e. - 153Sm,
$^{99m}$Tc, $^{51}$Cr, low for $^{113m}$In complex, and absolutely none for $^{64}$Cu-EDTMP, which moreover was dramatically unstable in vivo.

Table 1. Distribution of activity cumulated in rats tissue after 90 min post intravenous injection of EDTMP chelates (percent of activity cumulated in 1 g of tissue, N = 4 - 12)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$^{153}$Sm (III)</th>
<th>$^{99m}$Tc (IV)</th>
<th>$^{51}$Cr (III)</th>
<th>$^{113m}$In (III)</th>
<th>$^{64}$Cu (II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood 1 ml</td>
<td>0.04 ± 0.00</td>
<td>0.15 ± 0.02</td>
<td>0.09 ± 0.00</td>
<td>0.36 ± 0.10</td>
<td>0.10 ± 0.03</td>
</tr>
<tr>
<td>Lung</td>
<td>0.04 ± 0.02</td>
<td>0.12 ± 0.06</td>
<td>0.04 ± 0.01</td>
<td>0.26 ± 0.08</td>
<td>0.14 ± 0.02</td>
</tr>
<tr>
<td>Liver</td>
<td>0.07 ± 0.00</td>
<td>0.06 ± 0.01</td>
<td>0.08 ± 0.05</td>
<td>0.29 ± 0.05</td>
<td>3.97 ± 0.22</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.07 ± 0.00</td>
<td>0.05 ± 0.02</td>
<td>0</td>
<td>0.62 ± 0.24</td>
<td>0.11 ± 0.04</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.46 ± 0.07</td>
<td>1.66 ± 0.31</td>
<td>0.49 ± 0.09</td>
<td>0.59 ± 0.29</td>
<td>2.56 ± 0.33</td>
</tr>
<tr>
<td>Femur</td>
<td>6.07 ± 0.70</td>
<td>5.15 ± 0.31</td>
<td>4.83 ± 0.50</td>
<td>2.39 ± 0.45</td>
<td>0.16 ± 0.04</td>
</tr>
<tr>
<td>Activity in urine</td>
<td>49.89 ± 4.47</td>
<td>57.86 ± 4.35</td>
<td>43.07 ± 9.85</td>
<td>48.20 ± 4.32</td>
<td>8.23 ± 2.81</td>
</tr>
</tbody>
</table>

The positive change of activity deposition, quick activity clearance from blood and soft tissue, and high positive change of bone to liver ratio during the time of biodistribution, pointed out favourable behaviour of the samarium and technetium complexes (Table 2).

Table 2. Change of deposition and clearance of the complexes activity between 30 and 90 minutes post injection ([%A 90 min - %A 30 min]/%A 30 min)

<table>
<thead>
<tr>
<th>Complex</th>
<th>Bone</th>
<th>Blood</th>
<th>Liver</th>
<th>Bone/Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{153}$Sm-EDTMP</td>
<td>47.0</td>
<td>-93.2</td>
<td>-53.3</td>
<td>214.9</td>
</tr>
<tr>
<td>$^{99m}$Tc-EDTMP</td>
<td>30.4</td>
<td>-69.4</td>
<td>-50.0</td>
<td>160.8</td>
</tr>
<tr>
<td>$^{51}$Cr-EDTMP</td>
<td>19.0</td>
<td>-75.0</td>
<td>-33.3</td>
<td>78.4</td>
</tr>
<tr>
<td>$^{113m}$In-EDTMP</td>
<td>29.2</td>
<td>-35.7</td>
<td>0.0</td>
<td>29.2</td>
</tr>
<tr>
<td>$^{64}$Cu-EDTMP</td>
<td>-33.3</td>
<td>-37.5</td>
<td>3.4</td>
<td>-35.5</td>
</tr>
</tbody>
</table>

Our results indicate simplicity of EDTMP chelates formation with different metallic radioisotopes. Variety of EDTMP chelates, studied and described in literature, showed high bone deposition. However, the significant differences in stability in vivo we observed in our study, indicates that the properties of central metal ion implicates the biological behaviour of the complex in spite of high affinity of EDTMP to bone.

The appropriate selection of the radioactive central ion may make full use of an excellent properties of EDTMP ligand, which we conclude may play soon a dominant role as the favourable chelating agent with widely usage for diagnosis and therapy of bone diseases.

Reference

Trials to optimize dosimetry for $^{153}\text{Sm-EDTMP}$-therapy to improve therapeutic effects

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$^{153}\text{Sm-EDTMP}$ is used since years for pain reduction in patients with disseminated bone metastases [1], recently it is also been applied for therapy of inflammatory joint diseases [2]. Satisfactory therapy results were reported in 66 - 80 % of treated cases, the radiopharmaceutical was applied in “doses” of MBq/kg body weight. Considering the different extent of bone lesions and varying uptake patterns the differing and not optimal response rates could possibly improved by an individually performed dosimetry before therapy.

Material and Methods

Overall 30 patients were treated with $^{153}\text{Sm-EDTMP}$ (22 cancer patients, 8 patients with polyarthritis) 34 times. They received 18 - 55 MBq/kg body weight $^{153}\text{Sm-EDTMP}$. Using SPET and a MIRD-dosimetry [3] it was tried to estimate dose (Gy) to bone lesions after whole body scans with $^{99m}\text{Tc-DPD}$ ($n = 8$) and $^{99m}\text{Tc-EDTMP}$ ($n = 1$) assuming incorrectly a homogenous uptake in bone lesions. Then a dose-response relationship should established. Tumor volumes obtained by SPET were checked by Jaszak-phantom studies. The relative uptake of $^{99m}\text{Tc-DPD}$ and $^{99m}\text{Tc-EDTMP}$ in bone lesions, normal bone and soft tissues was analyzed using the ROI-technique on conjugated views of whole body scans. In 17 patients also whole body retention by measuring 24 hr. urine excretion of $^{99m}\text{Tc-DPD}$ and $^{99m}\text{Tc-EDTMP}$ was assessed and compared with retention of $^{153}\text{Sm-EDTMP}$. Therapeutic effects were assessed by careful follow-up over up to 2 yrs. and classified as “good” (++) , “satisfactory” (+) and “no response” (-).

Results

24 hr. retention of $^{99m}\text{Tc-phosphonates}$ and $^{153}\text{Sm-EDTMP}$ was comparable ($70.5 \pm 0.2 \%$ vs $68.2 \pm 0.1 \%$). Tumor volumes varied from 151 - 652 ml ($x \ 280$ ml) as well as count rates over tumor and normal bone (1.72 - 2.41).

Posttherapy scans after $^{153}\text{Sm-EDTMP}$ showed identical patterns as pretherapeutic $^{99m}\text{Tc scans}$ (Fig. 1). Uptake in metastases varied between 15 - 57 % of the doses. Table 1 shows obtained results applied activities and estimated radiation dose to bone lesions. There was no correlation between amount of activity applied and response to therapy but the vast majority of good responses were obtained with > 10 Gy. Overall 35.5 % had a “good” response, 38.2 % a “satisfactory” response and 11.8 % showed no response. In 14.7 % no follow-up was possible. Side effects were thrombopenia ($n = 6$) or leukopenia ($n = 6$) which required treatment only in 2 patients. We always noted a drop in alkaline phosphatase and in rheumatic patients of inflammation parameters, tremor marker levels decreased.

Fig. 1. Identical uptake of $^{153}\text{Sm-}$ and $^{99m}\text{Tc-phosphonate}$ ($^{153}\text{Sm left, }^{99m}\text{Tc right}$) in disseminated bone metastases of breast cancer.
transiently also in the majority of cancer patients.

**Discussion and conclusion**

The dosimetric approach to $^{153}$Sm-EDTMP therapy described in our study should be further evaluated in prospective studies and possibly corrections for inhomogenous uptake of the radiopharmaceutical in lesions can be made. It seems likely that > 10 Gy corresponds in reality to 30 - 40 Gy in tissue with $^{153}$Sm-EDTMP uptake. If one would increase doses, however, an even higher rate of success but also of myelotoxicity could occur. Bone marrow damage could possibly controlled by autologous transplantation of stem cells harvested prior to therapy while higher success rates would be a positive feature of such an approach.

**Table 1. Results dosimetric therapy trial with $^{153}$Sm-EDTMP**

<table>
<thead>
<tr>
<th>Pat.</th>
<th>Ca. type</th>
<th>MBq applied</th>
<th>Tu. Volume (ml)</th>
<th>Gy</th>
<th>effect</th>
<th>side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.B.</td>
<td>Breast</td>
<td>4,958</td>
<td>410</td>
<td>4.0</td>
<td>++</td>
<td>(+)</td>
</tr>
<tr>
<td>B.R.</td>
<td>Prostate</td>
<td>3,811</td>
<td>226</td>
<td>9.2</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>D.A.</td>
<td>Prostate</td>
<td>3,441</td>
<td>503</td>
<td>5.1</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>S.C.</td>
<td>Prostate</td>
<td>3,885</td>
<td>652</td>
<td>13.7</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>P.E.</td>
<td>Prostate</td>
<td>3,380</td>
<td>421</td>
<td>10.0</td>
<td>++</td>
<td>(+)</td>
</tr>
<tr>
<td>H.D.</td>
<td>Breast</td>
<td>2,793</td>
<td>350</td>
<td>11.0</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>A.G.</td>
<td>Breast</td>
<td>2,960</td>
<td>302</td>
<td>6.0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>H.O.</td>
<td>Breast</td>
<td>2,479</td>
<td>151</td>
<td>2.8</td>
<td>+</td>
<td>(+)</td>
</tr>
</tbody>
</table>

++ = good   + = satisfactory   ? = no follow up (+) moderate, transient thrombopenia

**References**

Radiopharmaceuticals of DTPA, DMSA and EDTA labelled with Holmium-166

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2Production Division, Department of Radioisotopes, Japan Atomic Energy Research Institute Tokai-mura, Naka-gun, JAPAN

Small amounts of holmium oxide were irradiated for 30 minutes at a flux of about $10^{14}$ n.cm$^{-2}$.s$^{-1}$ in the hydraulic rabbit (position 2) of the JRR-3 reactor at Tokai. The specific activity of the targets varied from 127 to 339 MBq/mg of Ho. After cooling them over varied lengths of time the targets were handled in a hot cell and later on removed to a shielded fume cupboard for processing and labelling.

The irradiated material was converted to chloride and nitrate forms in both aqueous and saline media during processing. DTPA and DMSA were added in the solid form and EDTA as an aqueous solution. The solutions containing DTPA and DMSA were warmed on a hot plate till a clear solution was obtained.

The chloride solutions of all the three complexes were adjusted at pH 2-3 and 5-6, and the nitrate ones at 3-3.5. In order to compare by chromatography the yield percent of the labelled compounds, blanks of chloride and nitrate were prepared without any ligand. The blanks were thus of pure $^{166}$HoCl$_3$ and $^{166}$Ho(NO$_3$)$_3$. No blank was prepared at pH 2-3.

The complex solutions and the blanks were allowed a reaction time of 30 minutes after pH adjustment. They were then spotted on cellulose plates and developed for about two and half hours in a solvent of pyridine, ethanol and water. The $^{166}$Ho[EDTA] complex was spotted on Whatman no.1 paper and developed like the other complexes.

After drying them in air the chromatograms were analysed in a scintillation detector (Ambis 100, Perkin Elmer) to determine percent labelling. The results showed that DTPA was labelled over 98, DMSA at about 90 and EDTA at 100.0%, respectively, with 166Ho.

The complexes were analysed the next day at 20-24 hours of reaction time to examine in vitro stability. Labelling was about the same as found after 30 minutes indicating good stability.

The chloride complex in saline of Ho[DTPA] was injected in an inactive state into the tail vein of three SD rats. The rats were sampled 30 minutes, four hours and 24 hours post-injection. The target organs were freeze dried and weighed amounts of organs irradiated. Biodistribution study in the rats showed an initial localisation in blood, lung and kidney of the chloride complex of $^{166}$Ho[EDTA] at 30 minutes of sampling. After four hours the labelled complex was found to have cleared from blood and lung, and localized 100% in kidney where it was found stable at 24 hours of sampling.

An aqueous solution in chloride of $^{166}$Ho was analysed in an HPGe detector to examine radionuclidic purity of the irradiated holmium oxide. No other nuclide was found present (Fig. 1) in the target except that of $^{166}$Ho.
Fig. 1.  Gamma spectrum of $^{166}$Ho
Studies on the preparation and evaluation of colloidal chromic phosphate - $^{32}$P for possible therapeutic use

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Introduction

Radionuclide therapy has become the focus of recent attention in nuclear medicine and three areas can be identified as of primary interest. The well established treatment of thyroid disorders with radioiodine has been complemented by impressive success in palliative treatment of metastatic bone pain, promises of radiation synovectomy and prospects of the recent efforts at targeted therapy based on both biological concepts and physico-chemical principles [1]. Amongst the suitable radionuclides being investigated, pure beta emitter $^{32}$P has continued to receive attention due to its easy economic availability and reasonably satisfactory nuclear characteristics [T1/2 14.3 d; $E_\beta$ (Max.) & (Ave.) 1.7 & 0.695 MeV, respectively; Range in tissue (Max.) & (Ave.) 8 & 3 mm, respectively]. In fact, the revival of interest in using $^{32}$P for treating metastatic bone pain and the satisfactory results demonstrated in nuclear medicine centres in India [2] have led to a resurgence of interest in seeking to use $^{32}$P for other applications, otherwise given up long back [3]. Due to such revived interest evinced by user physicians in India, an attempt has been made in our laboratory to standardise methods for preparation and evaluation of colloidal chromic phosphate - $^{32}$P suitable for therapeutic use. The applications could, in principle, cover not only the earlier established treatment of pleural and peritoneal effusions secondary to primary malignancy, but also radiation synovectomy and possible treatment of liver tumours (all by local instillation of the product).

Experimental

The radionuclides $^{32}$P and $^{51}$Cr were available as phosphoric acid (no-carrier-added) in HCl and as sodium chromate solution (~300 $\mu$Ci/$\mu$g), respectively, ex-stock in our Centre. All the chemicals used were from standard commercial sources. Radioactivity measurements were made in pre-calibrated ionisation chamber (NPL, UK) / radioisotope dose calibrator (ECIL, India and Capintec, USA) for samples in suitable activity range, while standard scintillation counter was used in the case of chromatographic supports and dialysate samples. Paper chromatography over Whatman 1 and water solvent recommended in USP [4] was employed for estimation of both radiochemical purity of the radiocolloid and its stability.

The procedure for colloid formation was adopted from the method of Anghileri [5] with modifications. In short, the present method involved reacting chromic acid with phosphoric acid (carrier added) in the presence of a reducing agent (sodium sulphite) and working up the reaction mixture (by dialysis / by centrifugation) to remove soluble phosphate and then suspend the final colloid formulation in an appropriate vehicle like 30% dextrose (suggested in USP [4]). The standardisation of reaction conditions was made initially using $^{51}$Cr tracer to follow the reaction, due to the relatively greater ease of gamma detection, especially at low levels of radioactivity. The finer adjustments were later done directly with $^{32}$P used in tracer level to follow the fate of soluble phosphate as well as quantify the same. A number of batches of colloidal chromic phosphate - $^{32}$P was prepared using the recipe standardised and the product evaluated for its stability and purity.

Results and discussion
It was possible to obtain about 60% yield of the colloidal product. The radiochemical purity of the final suspension of colloidal $^{32}$P was over 98%. The recourse to dialysis adapted in the present study, as against the centrifugation suggested in literature, gave slightly reduced recovery after purification; however, it was found to be more convenient to practise, in particular behind radiation shielding and advantageous for improved purity. Further, the colloid purified by dialysis was found to be more stable and the extent of in vitro leaching was less significant. In contrast, several steps of washing and centrifuging were needed for ensuring acceptable purity while following the earlier procedure. The new procedure is adaptable for handling large scale batches involving even a few hundred mCi levels of $^{32}$P. The results of particle size distribution and stability on storage vis-à-vis applicability for possible therapeutic use are analysed. Attempts to influence the particle size and establish protocol for biological studies to prove therapeutic utility and assess the release from instilled sites into circulation / location in non-target site(s) are underway and will be presented.

Acknowledgments

The authors thank Dr. S. Gangadharan, Chief Executive, BRIT for encouragement, Mr. M. Ananthakrishnan, Senior Manager (Radiochemicals), BRIT for providing the raw material radionuclides of $^{32}$P and $^{51}$Cr and all our colleagues in the Quality Assurance & Product Development (RPh) Group, Radiopharmaceuticals Programme, BRIT for their keen interest and co-operation.

References

MAG2GABA-Biocytin synthesized with new intermediates for radiolabeling $^{99m}$Tc and $^{188}$Re

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Avidin-biotin system is widely used in medical research, especially in pretargeting radionuclide therapy. $^{188}$W-$^{188}$Re generator is recently introduced in therapeutic nuclear medicine and made it possible to use whenever needed. $^{188}$Re can be labeled with biotin, peptides and other compounds for in vivo targeting.

A simple route for the facile synthesis of tetradentate bifunctional ligand which are very widely used in nuclear medicine field was developed for labeling biotin and peptides with $^{99m}$Tc and $^{188}$Re [1]. The new key compound, N-hydroxysuccinimidyl ester of S-benzoylmercaptoacetyldiglycine (NHS-MAG2) was synthesized first and reacted with $\gamma$-aminobutyric acid to give MAG2GABA. This MAG2GABA N3S chelator was then converted to NHS-MAG2GABA and conjugated to biocytin to give the MAG2GABA-Biocytin (MGB).

![Scheme of $^{188}$Re-MAG2GABA-Biocytin complexes](image)

For the labeling of home-made MGB with $^{99m}$Tc, MGB 10 µl MGB (20 mg/ml in DMSO) and stannous tartrate 10 µl (1 mg/ml) were added to a vial containing 50 µl 1M sodium potassium tartrate (pH 7). Then, 1 ml (10 mCi) $^{99m}$Tc pertechnetate was added [2]. And heated for 10 min at 100°C. For the $^{188}$Re labeling, 10 µl MGB (20 mg/ml in DMSO) was added in reaction vial, followed by the addition of 200 µl 1M sodium potassium tartrate (pH 7), 200 µl stannous tartrate (10 mg/ml) and 10 mCi $^{188}$Re perrhenate. Finally the reaction mixture was heated for 30 min at 100°C. Colloid were determined with ITLC-SG (Gelman) developed with MeOH:PBS (1:1). The reactant was purified with a C18 Sep-Pak cartridge. First, cartridge was eluted with 0.001N HCl to eliminate impurities. Labeled compound was eluted with EtOH:saline (1:1). HPLC analysis of the $^{188}$Re-labeled and $^{99m}$Tc-labeled MGB was performed on RP C18 column with a gradient mixture of methanol and 10 mM phosphate buffered saline (pH 7.4) at a flow rate of 1 ml/min. From 0 min to 10 min, 20% methanol was changed to 50% methanol. Until 20 min, the concentration of methanol was maintained to 50%. The retention time was about 13 min on radiochromatogram, colloid was below 1% and labeling yield was 95% for both $^{99m}$Tc and $^{188}$Re. Stability at 6 hour were both above 90%, at 30 hour $^{188}$Re-MGB was above 80%. Binding to streptavidin was confirmed by HPLC with TSK 4000 size-exclusion column.
The synthesis may be applied to preparation of positional isomers of MAG3-type ligand containing diverse carboxy terminal residue in place of glycine. This simple synthesis may be used to prepare new bifunctional chelators with unique properties related to carboxy terminal residue. MGB was labeled with $^{99m}$Tc and $^{188}$Re for scintigraphy and radiotherapy, using radiolabeled biotin, avidin-biotin system (three-step targeting) has been applied to enhance tumor to normal tissue ratios [3]. Radioimmunotherapy with pretargeting, can reduce non-specific radiation to normal tissues.

![Fig. 2. Reverse phase HPLC radiochromatogram of $^{188}$Re-MGB after reaction (30 min at 100°C)](image)

**Reference**


Dosimetry in radionuclide therapy

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The Radionuclide Therapy Committee of the European Association of Nuclear Medicine states correctly in the introduction to it’s protocols that therapeutic effects of radionuclides in the management of disease are due to the amount absorbed radiation energy and to the radiosensitivity of the irradiated tissue [1]. Absorbed radiation dose (= Gy), however, is frequently replaced in practical Nuclear Medicine by “mCi” or “MBq” as dose units, even as certainly the amount of activity applied is certainly not the only factor in delivery of an absorbed radiation dose. Radiation dose to an organ or tumor is defined by the simple equation:

\[ \text{Gy} = \frac{\text{activity} \times \text{residence time (t)} \times S}{\text{volume}} \]  

[2]. The specific S-value of a radionuclide refers to linear energy transfer of it’s radiation including also relative biological weighting factors. It would seem logical to establish a clear dose response relationship for Nuclear Medicine therapy (Table 1), so that adequate clinical results could be expected. Specific modalities especially of systemic radionuclide therapy, however, make dosimetry and therefore an estimate of the dose response relationship quite difficult.

Table 1. Estimated correlation of radiation dose with degree of radiation atrophy

<table>
<thead>
<tr>
<th>radiation dose</th>
<th>radiation effect</th>
<th>clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 - 100 Gy</td>
<td>moderate atrophy</td>
<td>metabolic activity significantly reduced, growth potential impaired, moderate volume reduction of irradiated tissue</td>
</tr>
<tr>
<td>100 - 150 Gy</td>
<td>significant atrophy</td>
<td>metabolic activity severely reduced, growth potential blocked, significant volume reduction of irradiated tissue</td>
</tr>
<tr>
<td>200 - 300 Gy</td>
<td>severe atrophy</td>
<td>metabolic activity and growth potential blocked, volume of irradiated tissue: almost gone</td>
</tr>
<tr>
<td>500 Gy</td>
<td>necrosis</td>
<td>tissue dead and gone</td>
</tr>
</tbody>
</table>

In Nuclear Medicine there is only one therapeutic method which allows a dosimetric calculation as in other forms of radiotherapy: This is radioembolization of hepatoma with $^{90}$Y-particles [3]: The tumor (= target) volume is known from CT-scans, 100 % of the selectively intraarterially applied activity are in the tumor, no metabolic break-down of the labeled particles occurs for several physical halflives of $^{90}$Y so that “residence time” equals physical halflife. Even intratumoral application of radioactive colloids which should stay in the tumor does not fit in this model, as intratumoral distribution is variable.

Also in all other therapeutic methods (intracavitary, systemic) such assumptions are not correct: Definition of target volume, residence time can vary and in systemic therapy also the amount of activity delivered to the target. Target volume can be assessed by sonography, CT, MRI, SPECT and PET for solid lesions, it’s assessment in intracavitary therapy is almost impossible. Target volume can also not be assessed in cases with diffuse bone marrow involvement (bone metastases with “superscans”, patients with neuroblastoma in bone marrow etc.). Residence time can easily be registered when the radiopharmaceutical emits $\gamma$-radiation.
by serial activity measurements over the target. It is impossible to evaluate this parameter when pure β-emitters are used. The same situation exists when activity delivered to the target should be estimated. For β-emitters identical γ-emitting radiotracers can be used for this purpose (e.g. $^{85}$Sr for $^{89}$Sr, $^{111}$In-Octreotide for $^{90}$Y-Octreotide). Activity delivered to the target can be estimated for γ-emitters (e.g. $^{131}$I, $^{153}$Sm, $^{186}$Re) by quantitative scans and SPECT [4] or by substitution of such radionuclides with PET-tracers (e.g. $^{124}$I). For pure β-emitters one can again substitute a PET-tracer (e.g. $^{86}$Y for $^{90}$Y). Overall therefore, we do have possibilities to estimate uptake of the radiopharmaceutical, target volume (Fig. 1) and residence time for many therapeutic methods and we should make use of them to achieve some gross dosimetry. $^{86}$Y would even provide a possibility to measure target volume for intracavitary therapy. Similar dosimetric approaches should also be applied to predict side effects of radionuclide therapy due to irradiation of bone marrow and critical organs. Recent insights of microdosimetry, however, including effects of Auger electrons and α-emitters cannot adequately be used in clinical therapy in general as yet. The mentioned dosimetric methods are not very popular in large parts of the Nuclear Medicine Community as it is known that simple empirical strategies such as "fixed dose"-applications (e.g. $^{131}$I, $^{89}$Sr, $^{32}$P) have been quite successful also. This discrepancy between results of scientific dosimetry and clinical outcome without it can partly be explained by differences in individual radiosensitivity.

The assessment of specific radiosensitivity of a lesion is still an unsolved problem. Studies using Palladium-islets or well plates were done [5] but results so far show, that it still is almost impossible to register e.g. radiosensitivity of a certain tumor in an individual patient. While the efforts to improve registration of specific radiosensitivity by ex-vivo assays should be encouraged in the future one should also try to overcome the old habit of using only amounts of radioactivity as "doses" especially as new and exciting therapeutic applications of radionuclides are being developed. In this situation one should try at least to estimate absorbed radiation dose (= Gy) in therapy, which could improve results of our therapeutic approaches significantly.

References

Bone pain palliation with $^{32}$P therapy

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$^1$Department of Radiotherapy

$^2$Department of Nuclear Medicine, National Oncology Centre, Sofia, BULGARIA

Palliation of pain from multifocal bone metastases in patients with breast and prostate cancers is a serious problem.

The aim of this study has been to determine the efficiency of pain palliation with $^{32}$P of patients suffering from bone metastases due to breast and prostate cancer.

Bone metastases are found predominantly in the axial skeleton and include the vertebral bodies, pelvis and ribs, followed by the sternum, skull, femora and humeri. The tendency of prostate and breast cancer is to produce metastases in the axial skeleton.

Sterile non-pyrogenic solution of orthophosphate produced by Polatom $^{32}$P was used for palliative treatment of painful metastatic bone disease. 114 patients (pts) mean age 67; range 48-76 entered the study. 93 patients were with breast cancer (41- with invasive intraductal, 29- with invasive lobular, 8- with adenoic cystic, 2- with mucinous, 4- with medullary carcinoma and 9 - with undifferentiated). The rest 21 pts had prostate cancer. The whole body of bone scintigraphy was carried out before and after the radiophosphorus treatment, using $^{99m}$Tc-MDP (555-740 MBq). All patients were with adequate haematological function (WBC $> 3.5 \times 10^9/1$ and PLT $> 140 \times 10^9/1$). These pts were treated with doses starting at 37 MBq and increasing to 222 MBq at intervals of 30-60 days. Patients having massive bone metastases underwent external beam radiotherapy ($5 \times 4 \, Gy$ or $2 \times 8 \, Gy$) in the regions of the spine and pelvis to prevent pathological bone fractures.

In 78% of the cases $^{32}$P therapy resulted in a symptomatic pain reduction with duration of response 3-6 months at the cost of no significant side effects. After the treatment objective response was obtained on the bone scintigraphy. Alkaline phosphate levels showed a significant decrease in the patients treated. Serum PSA and CA 15-3 values were reduced in 35% and 47% respectively.

Radiophosphorus is cost effective, easy to administer and localize in the most sites of bone metastases. Maximum administered dose of $^{32}$P (222 MBq) was effective for the palliative treatment in 78% of pts with painful bone metastases for 3-6 months.
32-Phosphorus for bone pain palliation due to bony metastases, its safety and efficacy in patients with advanced cancer

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Introduction

Metastatic involvement of the skeleton is common in patients with several types of cancer, especially prostate and breast cancer. A prominent symptom caused by bony metastases is pain, which can seriously affect patient’s quality of life. Pain palliation therapy using narcotic drugs and external hemibody irradiation causes considerable side effects, while prolonged treatment with polyphosphates is expensive. Therefore in many patients with a large number of lesions radionuclide treatment using single dose of beta emitting bone seeking radiopharmaceuticals has become widely accepted. 89-Strontium and several 186-Rhenium and 153-Samarium labeled polyphosphates have become available, but all of them are expensive and difficult to obtain in certain countries.

32-Phosphorus can be used for the same purpose \cite{1}, it is not expensive and is more accessible. It decays by beta radiation of maximum energy of 1.71 MeV with mean range of beta particles in tissue of 3 mm and maximum range of 8 mm. It’s physical half life is 14.3 days. It’s biological half life in the bone marrow is 7 - 9 days. Since it is incorporated into the nucleic acids of rapidly proliferating cells as well as into cortical bone concern was raised that bone marrow toxicity with possible severe consequences can outweigh benefit of bone pain palliation.

The aim

The aim of the study was to evaluate safety and efficacy of 32-P for palliation of bone pain due to bony metastases. For this purpose toxicity and efficacy of 32-P was compared with toxicity and efficacy of 89-Sr \cite{2}, the most commonly used radiopharmaceutical for bone pain palliation in the framework of a prospective IAEA coordinated multicentric study.

Patients and methods

A very strict protocol for unified patient inclusion and follow up was used. Patients were randomised to receive either 32-P (450 MBq 32-P as orthophosphate orally) or 89-Sr (150 MBq 89-Sr as chloride i.v.). 93 patients were included into the study, 68 males and 25 females with mean age of 62 years. Most patients had bony metastases due to prostate and breast cancer, lung, colorectal, ovarian, bladder and even thyroid cancer patients were also represented. Most patients were treated by surgery, chemotherapy, radiotherapy, and hormonal therapy as indicated previous to radionuclide therapy. 45 patients received 32-P and 48 89-Sr.

Efficacy was assessed 14 days before treatment and for 4 months after treatment as intensity of bone pain recorded once daily on 1 - 10 subjective scale, consumption of analgesics determined as type of analgesic multiplied by daily frequency (analgesic index), and general quality of life data.

Toxicity was also assessed 14 days before treatment and every 14 days after treatment for 4 months by measuring platelet count, total white blood cell (WBC) and differential count,
haemoglobin (Hb) concentration, and creatinine concentration. Presence of bleeding, infection, gastrointestinal problems etc. was recorded.

T-test and chi-square test for univariate comparison of treatment groups and Cox's proportional hazards model was used to calculate the duration of effects.

Results

The patients were classified as responders or not-responders at a meeting of all contributing investigators taking into account changes in individual pain score and analgesic index. Also duration of the favourable effect was determined in responders using the same criteria. 68% of all patients were considered to respond to treatment with radionuclides. 60% of patients responded to treatment with phosphorus and 75% to treatment with strontium. While difference between number of patients who responded favourably to 89-Sr and 32-P is not significantly different (p = 0.122), the probability of success in the 89-Sr treated group is 1.25 times greater than in the 32-P treated group (Table 1).

Table 1. Efficacy: No of patients treated with 32-P and 89-Sr with pain relief (Response)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>32-P</td>
<td>27 (60.0%)</td>
<td>18 (40.0%)</td>
</tr>
<tr>
<td>87-Sr</td>
<td>36 (75.0%)</td>
<td>12 (25.0%)</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>63 (67.8%)</td>
<td>30 (32.3%)</td>
</tr>
</tbody>
</table>

For responders duration of the response was also considered important. We compared the length of response between both treatment groups using the methods of survival analysis. The time of interest, 'survival time', was time elapsed between the beginning of the response and end of the response. At any time point proportion of patients still having good effect of treatment with each radiopharmaceutical is calculated. No significant differences between both groups was observed (p=0.737).

Other than changes in platelet and WBC counts and Hb concentration no adverse effects were observed in either group. Greater proportion of decrease for all three haematological parameters was observed in the group of patients treated with 32-P than with 89-Sr. Decrease of WBC and platelet counts were recorded significantly more often in patients treated with phosphorus than with strontium while no statistically significant differences was seen in frequency of Hb concentration decrease (Table 2).

Table 2. Toxicity: No of patients treated with 32-P and 89-Sr with pathological decrease of WBC, platelets, and Hb concentration.

<table>
<thead>
<tr>
<th></th>
<th>32-P</th>
<th>89-Sr</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>45</td>
<td>48</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>19 (42%)</td>
<td>9 (19%)</td>
<td>28 (30%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Platelets</td>
<td>25 (56%)</td>
<td>16 (33%)</td>
<td>41 (44%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Hb</td>
<td>31 (69%)</td>
<td>26 (54%)</td>
<td>57 (61%)</td>
<td>0.145</td>
</tr>
</tbody>
</table>
Discussion

Both 89-Sr and 32-P are used mainly to suppress hyperproliferative cell lines rather than to eradicate them, therefore expected effect of such treatment is predominantly palliation of bone pain rather than treatment of bony metastases. Favorable response to treatment was recorded in 75% of patients treated with 89-Sr and in 60% of those treated with 32-P, overall response being 67.8%. These values are in accordance with published figures for success of bone pain palliation using radionuclides in patients with different types of cancer [2]. There was no significant difference between the duration of favorable effect for both radiopharmaceuticals.

Limiting side effects using radiopharmaceuticals is temporary myelosuppression, the severity of which can be influenced also by the extent of tumour involving bone marrow, previous radiotherapy and chemotherapy as well as patient’s general condition. Moderate decrease of lymphocytes, granulocytes, platelets, and hemoglobin levels was detected, and although decrease of WBCs and platelets in 32-P treated group was statistically significantly more prominent than in 89-Sr treated group, it was clinically not considered important, since no toxic effects requiring specific treatment were seen in either group.

Conclusion

According to our results 32-P is slightly but not significantly less effective than 89-Sr for palliation of bone pain due to bony metastases. Although 32-P appears to be more toxic it is important to note, that no toxic effects requiring specific treatment were seen in either group. It seems to be as safe as 89-Sr using doses up to 450 MBq. Due to its comparable efficacy and toxicity, general availability and low cost its more widespread use should be encouraged to increase quality of life and reduce cost of medical care of patients with intractable bone pain due to cancer metastases.

References

Therapy with strontium-89 for bone pain palliation in prostate cancer patients

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Nuclear Medicine Department, Instituto Português de Oncologia Francisco Gentil, Lisboa, PORTUGAL

Prostate cancer is a major public health problem, since it is one of the most frequent tumors in males and is the fifth most common cause of cancer death throughout the world. The morbidity following skeletal involvement is high. The major clinical problem for most patients with metastatic disease is the severe bone pain. The mainstay of treatment for bone metastases of prostatic origin is some form of hormonal manipulation. However, eventual escape from hormonal control is inevitable in the majority of patients. Thereafter, the prognosis is poor, with a survival ranging from 4 to 8 months, and therapy is confined to palliative and symptomatic pain control. A wealth of data supports the clinical use of strontium-89 ($^{89}$Sr) chloride as an effective agent for the palliation of painful osseous metastases. We evaluated 56 patients with bone metastases secondary to prostate cancer treated with 4 mCi (150 MBq) of strontium-89 administered intravenously, in terms of efficacy and safety.

All patients included in this review have been diagnosed with a prostatic cancer, histologically confirmed with an expected survival of at least three months. Furthermore, all patients have bone metastases, as demonstrated by bone scan imaging in the three months preceding therapy. In 13 patients, the number of bone metastases was equal to or less than 5 (23%) - Group A, and the remaining (43 pts) presented with more than 5 metastases (77%) - Group B.

Each patient was submitted to a pre-therapy interview in which the clinical situation is reviewed and the indication for $^{89}$Sr therapy is evaluated, based on the presence of bone pain of metastatic origin, and also hematological parameters and renal function. Platelets counts should be more than 60,000/mm$^3$ and white cell count more than 2400/mm$^3$. Serum creatinine should be less than 1.5 mg/dl.

After therapy, the patients return for a monthly follow-up examination, in which a questionnaire to evaluate the intensity of pain and its effects on the quality of life, including analgesic consumption, is filled out. Safety is evaluated by monitoring hematological parameters and renal function, as well as any other adverse effects which might occur.

Therapeutic efficacy was evaluated in 49 patients. At three months, an improvement in symptoms (reduction/disappearance of pain) was reported after 28 therapies (57%). After twenty-one therapies (43%) no improvement was reported. In Group A (11 cases) 8 therapies were effective (73%). On the other hand, in group B (38 cases), only 20 pts reported an improvement (53%). It was possible to determine the time at which an improvement occurred after 24 therapies. Pain relief was reported in the first month post-therapy in 75% of cases (18 therapies) and in the second month in the remaining 25% (6 therapies). There were no cases of relief or reduction of pain in the third month. We were able to evaluate the hematological parameters after 40 therapies (11 from Group A and 29 from Group B). Reductions in cell counts were considered significant if equal to or greater than 20% in comparison to the pre-treatment values. A reduction in hemoglobin value was observed after 5 therapies (12% of cases), in white cell count after 21 therapies (53%), and in platelet count after 30 therapies (75% of therapies). In Group A (n = 11) there was a reduction in WBC count after 5 therapies
(45%) and in platelet count after 9 therapies (82%). In Group B (n = 29), there was a reduction in WBC count in 16 cases (55%) and in platelet count in 19 cases (66%).

It was possible to determine the time at which the reduction in WBCs (21 therapies) and platelets (27 therapies) occurred. The decrease in WBC count occurred in the first month post-therapy in 13 cases (62%) and in the second month in the remaining 8 cases (38%). Platelet reductions were observed in the first month in 24 therapies (89%), in the second month in 2 cases (7%), and in the third month in one case.

The evolution of bone metastases was evaluated after 21 therapies, by means of bone scans performed pre-therapy and 3 months post-therapy. Considering only the number of metastases, we observed no change in 16 cases (76%); there was an increase in the number of lesions after 5 therapies (24%); there was no decrease in the number of lesions in any of the pts.

PAIN EVALUATION QUESTIONNAIRE

INTENSITY OF PAIN
0 without pain
1 sporadic pain
2 mild, but constant pain
3 moderate pain
4 intense pain

Painkiller intake ....... DAILY
.................. OCCASIONAL
.................. NEVER

PAINKILLERS USED : ...........................................

References
New aspects of radionuclide therapy of bone and joint diseases

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In 1940/41 a patient with prostate cancer and painful osteoblastic bone metastases was treated with 8 mCi Sr-89 with positive effect concerning pain by C. Pecher. In Europe about 55 new patients/100,000/year with prostate cancer and 114 new patients/100,000/year with breast cancer are diagnosed. By autopsy in about 80% of patients with prostate cancer and 75% of patients with breast cancer bone metastases were observed. 30% of patients with bone metastases develops severe pain syndrome which needs therapy. For radionuclide therapy for pain palliation because of bone metastases in Europe 3 radionuclides are available: Sr-98, Sm-153, and 186-Re. Whereas Sr-89 exchange with calcium component of hydroxiapatite, the more recently available radiolabeled bisphosphonates (Sm-153-EDTMP and Re-186-HEDP) localize in bone by bridging the hydroxiapatite. The amount of uptake depends on metabolic activity of normal bone and tumor tissue.

**Physical characteristics**

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Pharmaceutical</th>
<th>half life (days)</th>
<th>maximum $\beta$ energy MeV</th>
<th>means $\beta$ energy MeV</th>
<th>maximum range in tissue(mm)</th>
<th>$\gamma$ Photon keV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sr-89</td>
<td>chloride</td>
<td>50.5</td>
<td>1.46</td>
<td>0.583</td>
<td>6.7</td>
<td>-</td>
</tr>
<tr>
<td>Sm-153</td>
<td>EDTMP</td>
<td>1.95</td>
<td>0.8</td>
<td>0.224</td>
<td>3.4</td>
<td>103 (28)</td>
</tr>
<tr>
<td>Re-186</td>
<td>HEDP</td>
<td>3.8</td>
<td>1.07</td>
<td>0.349</td>
<td>4.7</td>
<td>137 (9)</td>
</tr>
</tbody>
</table>

Prior to the administration of the radiopharmaceutical agents increased osteoblastic activity in the metastases should be documented by bone scintigraphy.

**Indications:**

Strontium-89 chloride, Sm-153 EDTMP and Re-186 HEDP (and the other unsealed beta-or conversion electron-emitting radiopharmaceuticals under development or available commercially, i.e. P-32- orthophosphate, 117m-Tn-DTPA, Re-118) are indicated for the treatment of bone pain due to a metastatic malignancy that has involved multiple skeletal sites and has evoked an osteoblastic response on bone scintigraphy. Where there is danger of either spinal cord compression from vertebral metastases or pathologic fracture in the extremities, radionuclide therapy for pain palliation should only be used in conjunction with other forms of management directed at these complications.

In general, patients should not have received long-acting myelosuppressive chemotherapy for 6-8 weeks or systemic radiotherapy for approximately 4 weeks prior to administration of Sr-89 and for 6-12 weeks after Sr-89 administration because of the potential for severe leukopenia or thrombocytopenia. Caution should be used if Sr-89 is used in conjunction with myelosuppressive chemotherapy. In patients to be treated with Sm-153 or Re-186 the intervals could be shorter, depending on blood cell counts. The patient should not have received external beam hemibody radiation within 2-3 months prior to administration of Sr-89, Sm-153 or Re-186 to reduce the probability of combined myelotoxicity from the external and internal radiation sources during this period.

Complete blood counts should usually be obtained within 7 days prior to administration of Sr-89, Sm-153 or 186-Re. The patient’s platelet count should probably exceed 60,000 and preferably 100,000/ml; the leukocyte count should probably exceed 2,400 - 3,000 and preferably 5,000/ml; and the absolute granulocyte count should exceed 2,000/ml to receive Sr-89, Sm-153 or Re-186. Results below these blood count levels are not absolute contraindications to treatment but raise the chance of infection or bleeding. Other contraindications are renal failure and active disseminated intravascular coagulation.
The usual administered activity of Sr-89 ranges from 1.5-2.2 MBq/kg (40-60 μCi/kg), of Sm-153-EDTMP 37 MBq/kg bodyweight and of Re-186-HEDP 1295 MBq. The procedure may be repeated 12 or more weeks, using Sr-89, 4-6 weeks using Sm-153 or Re-186 after the first injection if blood counts are at the suggested levels. The response rate after the first treatment is about 70 %, after the second treatment about 50 %.

Independent from the radionuclide used for pain palliation the onset of pain relief is more rapidly after Sm-153 or Re-186 administration than after Sr-89, but the mean duration of response after Sr-89 is longer (6 months vs. 3 months). That is why some centres prefer a “cocktail” treatment to optimize the effect of pain palliation without increasing the risk of primary adverse effects.

In animal experiments Sm-153 was used for curative treatment of primary bone tumors. Clinical dose escalation trial are running in some centres in the US and Europe treating metastases of primary bone tumors. Preliminary results are quite promising.

Radiosynovectomy is a well accepted therapeutic procedure in inflammatory joint diseases. There are several radionuclides available for this treatment.

**Physical characteristics:**

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Y-90</th>
<th>Re-186</th>
<th>Er-169</th>
</tr>
</thead>
<tbody>
<tr>
<td>phys. Half-life</td>
<td>64 h</td>
<td>90.6 h</td>
<td>9.4 d</td>
</tr>
<tr>
<td>mean range (soft tissue)</td>
<td>3.6 mm</td>
<td>1.2 mm</td>
<td>0.3 mm</td>
</tr>
<tr>
<td>max. range</td>
<td>11.0 mm</td>
<td>3.6 mm</td>
<td>0.7 mm</td>
</tr>
</tbody>
</table>

**Indications:**
- Rheumatoid arthritis
- other inflammatory joint diseases (except bacterial, tuberculous)
- persistent synovial effusion (knee prosthesis)
- pigmented villonodular synovitis
- haemophilic joint disease

**Activity, recommended for the joints to be treated:**

<table>
<thead>
<tr>
<th>Nuclide (MBq)</th>
<th>Y-90</th>
<th>Re-186</th>
<th>Er-169</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>185-222</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder</td>
<td>110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbow, ankle, wrist</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metacarpo-phalangeal</td>
<td>20-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metatarso-phalangeal</td>
<td>30-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>prox. interphalangeal</td>
<td>10-20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After nuclide administration the treated joint has to be immobilized for at least 48 hours. The results depend on the stage of the disease and bone destruction. The overall results in joints without severe destruction show an improvement in about 70-80%. Nearly same results were published for surgical synovectomy. First preliminary results in treatment of patients suffering from rheumatoid arthritis with Sm-153-EDTMP systemically are promising.
166Ho-hydroxy apatite particles for radiation synovectomy

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Development of new radiopharmaceuticals for the effective management of synovial inflammation and related arthritis problems are gaining attention. 166Ho, 153Sm, 186Re and 165Dy are some of the radioisotopes proposed for radiosynovectomy [1-3]. Hydroxy apatite, which is a natural constituent of bone has excellent bio-compatibility and hence has been selected as the carrier molecule by several groups for the above application [4-5]. 166Ho isotope can be easily made in high specific activities in a medium flux reactor and the present paper describes the preparation of HA particles, labelling them with 166Ho, characterisation of the complex and its stability studies in detail.

Production of 166Ho

166Ho is produced by irradiating 5 mg of 165Ho2O3 in Dhruva reactor for 7 days at a flux of 3x10^13 neutrons/cm^2.sec.

\[ ^{165}\text{Ho}(n,\gamma)^{166}\text{Ho} \rightarrow ^{166}\text{Er} \text{ (stable)} \quad (\sigma - 66 \text{ barns}, ^{165}\text{Ho} - 100\%) \]

\[ T_{1/2} = 26.9 \text{ h} \]

This resulted in the production of 28 GBq of 166Ho activity at the end of six hours after EOB(?) and the corresponding specific activity will be 6.3 TBq/g of Ho. Since a very high purity target was used, no other $\gamma$ emitting impurities were detected in MCA $\gamma$ spectrometry. Irradiated Ho2O3 was dissolved in 0.1 N HCl acid by gentle warming and directly used for labelling studies.

Synthesis of HA

HA particles were synthesised by a report method [6]. 79 gm (0.33 M) of Ca(NO3)2.4 H2O dissolved in 300 mL of double distilled water and 27 g (0.2 M) of (NH4)2HPO4 in 500 mL double distilled water were mixed together and the pH was adjusted to ~12. The solutions were mixed vigorously and the precipitate formed was heated for 10 minutes at 70°C. The precipitate was filtered and washed with 200 ml of hot double distilled water and dried initially at 150°C and then for 1 h at 240°C. After cooling, the precipitate was ground and sieved and particles in the appropriate range were taken for experiments.

Labelling

A 15 mg/mL solution of citric acid monohydrate was prepared in 0.1 N HCl. To 1 mL of this solution, 74-111 MBq of 166HoCl3 was added and the mixture was vortexed for 30 seconds and incubated for 30 minutes. At the end of 30 minutes, 200 $\mu$L of the complex solution was mixed with 40 mg of HA in a test tube and 800 $\mu$L d.d. water was added to it. The test tube was vortexed for 1 minute and kept for equilibration for 1 h in a shaker. The contents were centrifuged at 2000 rpm for 5 minutes. 0.5 mL of the supernatant was pipetted out and counted in a NaI(Tl) single channel counter and from this data, the labelling yields were calculated. 166Ho-HA particles were decanted off from the remaining solution and further mixed with 4 mL saline, vortexed and centrifuged at 2000 rpm for 5 minutes. 2 mL supernatant was taken out for counting to see any release of activity from the complex.
Radiochemical purity of the $^{166}\text{Ho}$-HA particles was ascertained by paper chromatography technique using Whatman 3MM chromatography paper and saline as the solvent. The complex was found to remain at the point of spotting and free $^{166}\text{Ho}$ moves along with the solvent front. The results of the optimisation studies are given in Tables 1 to 3.

**Table 1. Labelling yield as a function of the concentration of HA particles**

<table>
<thead>
<tr>
<th>Amount of HA</th>
<th>20 mg</th>
<th>40 mg</th>
<th>60 mg</th>
<th>80 mg</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Complexation yield</td>
<td>43.7</td>
<td>74</td>
<td>85.8</td>
<td>93.0</td>
<td>96.1</td>
</tr>
</tbody>
</table>

**Table 2. Effect of Citric acid concentration on complexation yield**

<table>
<thead>
<tr>
<th>Citric Acid (mg/mL)</th>
<th>5.0</th>
<th>10</th>
<th>30</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Complexation yield</td>
<td>99.1</td>
<td>91.7</td>
<td>68</td>
<td>39.1</td>
</tr>
</tbody>
</table>

**Table 3. Effect of pH on labelling yield (40 mg HA and 15 mg/mL of citric acid used for the reaction)**

<table>
<thead>
<tr>
<th>pH of reaction</th>
<th>4.0</th>
<th>7.0</th>
<th>9.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Complexation yield</td>
<td>83.8</td>
<td>99.5</td>
<td>95.5</td>
</tr>
</tbody>
</table>

The $^{166}\text{Ho}$-HA particles were found to be stable for 72 h as estimated by paper chromatography. The high complexation yield and good stability of the $^{166}\text{Ho}$ labelled particles indicate that these particles could be used for radiosynovectomy application. Biodistribution studies to find out the efficacy of these particles as radiosynovectomy agents are being planned.

**References**

Radiation synovectomy with samarium-153 particulate hydroxyapatite: A preliminary report

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²Pramongkutklao Hospital, Bangkok, THAILAND
³Office of Atomic Energy for Peace, Bangkok, THAILAND

Radiation synovectomy with various radiopharmaceuticals has been used to alleviate the pain and swelling of rheumatoid arthritis for more than 40 years. The procedure consists of the injection of a beta-emitting radiopharmaceutical into the joint space and some of the injected radioactivity is absorbed by phagocytic lining cells along the synovial surface. As radionuclide decays, regenerating synovium will be irradiated. Samarium-153 particulate hydroxyapatite (Sm-153 PHYP) which is recently used in this field, can be locally prepared by the Isotope Production Division, Office of Atomic Energy for Peace, Thailand. With 103 keV photon of gamma decay by Sm-153, extra-articular and intra-articular distribution of activity accumulation in patients can be assessed by gamma camera. We evaluated the biodistribution of Sm-153 PHYP from whole-body imagings in patients with chronic arthritis.

Materials and methods

Fourteen patients (age: 33-81 years; mean 57 years; F:M = 13:1) with active and persistent arthritis who were refractory to intra-articular steroid injection were enrolled. Pregnant or breast feeding females, patient younger than 18 years old and patients with extensive cartilage and bone destruction (Stage 3, 4 of Steinbrocker’s classification) were excluded.

Intra-articular injection of 15 mCi of Sm-153 PHYP was given by the rheumatologist as an outpatient therapy. To ensure the needle was in the correct intra-articular position, synovial tapping from the large joint through a 21-gauge needle was tried to do first. (Fluoroscopic guidance was necessary for the small joints.) Most of the effusion was removed as much as possible before the radiopharmaceutical was injected into the joint and flushed through with a mixture of 2% xylocaine and 10 mg of triamcinolone acetonide. The total minimum volume of injection was 5 ml for knee joint and 2 ml for ankle joint. In addition to make the volume of radiopharmaceutical solution fitted for the particular joint, xylocaine and triamcinolone acetonide were also helpful to minimize the transient local reaction and effusion after injection. The activity in the injection apparatus was measured both before and after injection. Immediately after injection, the joint was passively flexed to augment intra-articular distribution. The patients remained nonweight-bearing for 4 hours after injection. Patients were allowed to leave the department 4 hours postinjection and advised to rest but allowed to resume their normal activities the following day.

For extra-articular activity analysis, anterior and posterior whole-body imagings were acquired immediately and 72 hours following injection using a single-headed gamma camera (Toshiba GCA-901A) with a low-energy, high resolution collimator with a 20% window centered at 103 keV for Sm-153. For intra-articular distribution analysis, anterior and lateral static images of the injected joint were performed following the whole-body imaging. SPECT images were acquired in five cases.
Results

Sixteen intra-articular injections were performed (two patients received two injections, knee:ankle = 12:4). Mean injected activity was 19.04 mCi (range 6.97 - 28.92 mCi). The immediate and 72-hour whole-body imagings showed no extra-articular localization of activity in two patients (12.5%) (Fig. 1). Mean extra-articular activity accumulation was calculated from whole-body imaging data. In four patients (25%) activity was noted in the lung immediately after injection (mean 0.18% of injected activity) as shown in Table 1. In six patients (37.5%) and seven patients (43.75%), 0.17% and 0.09% of the injected activity accumulated immediately in the liver and the regional lymph nodes, respectively.

![Fig. 1. Anterior and posterior whole-body imagings immediate (left) and 72-hour (right) after Sm-153 PHYP synovectomy of the right knee show no extra-articular activity.](image)

### Table 1. Activity localization in different organs post radiation synovectomy

<table>
<thead>
<tr>
<th>Time following injection</th>
<th>Mean activity in different organs (% intra-articular injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lung</td>
</tr>
<tr>
<td>Immediate</td>
<td>0.18 (n = 4)</td>
</tr>
<tr>
<td>72-hour</td>
<td>0.19 (n = 5)</td>
</tr>
</tbody>
</table>

Discussion

Although there were extra-articular activity in many patients, the very low levels of the activity indicated that synovectomy with Sm-153 PHYP could be performed as an out-patient procedure. These findings differed from synovectomy using radiolabelled colloid in which the patients had to be admitted and immobilized in the hospital for 24-48 hours after injection. Local preparation of Sm-153 PHYP which has been supported by the International Atomic Energy Agency leads to an appropriate utilization of national resources and low expense. We believe that Sm-153 PHYP may be useful for radiation synovectomy as an out-patient procedure because the procedure is very easy and associated with low-extra-articular leakage.
References


Radiation synovectomy in chronic knee synovitis: Self experience and review of the literature

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The technique of radiation synovectomy has been available for more than 40 years for the management of joint diseases [1]. Recently there has been renewed interest in radiation synovectomy [2]. The most widely reported radiopharmaceutical in current use is yttrium-90 radiocolloid (90Y) [1]. A new radiopharmaceutical has been recently introduced which aims to replace the previously used colloid radiopharmaceutical: dysprosium-165 ferric hydroxide macroagregate. The use of the latter particulate radiopharmaceuticals theoretically offers consistently lower levels of extra-articular activity accumulation, resulting in safer and more precise therapeutic alternative to radiocolloids. However, the use of particulate radiopharmaceuticals needs further evaluation to prove its efficacy for future therapeutic option.

In a survey of radiation synovectomy in Europe in 119 institutions in 23 different countries [1], 8578 patients, post radiation synovectomy treatment, were clinically evaluated. Overall a 90Y radiocolloid had been used in 94% of the medical centers.

We present here our experience with radiation synovectomy using intra-articular injection of 90Y, together with a review of the literature on this subject. A special emphasis will be placed on the following questions:

1. The clinical efficacy of particulate versus colloid radiopharmaceutical, in different joints.
2. The response rate to single injection versus routine repeated injections of the radiopharmaceutical.
3. The clinical importance of some different techniques of treatment in different clinics, including injected dose, injection procedure, safety precautions, etc.
4. Comparison of the efficacy of radiation synovectomy to intra-articular corticosteroid injection, in different kinds of articular diseases, as well as in different joints and polyarticular versus monoarticular disease.
5. The use of different 90Y colloids (resin, citrate, silicate and ferric hydroxide), comparing especially the extent of regional lymph node irritation as a result of joint leakage.
6. The clinical importance of co-injection of corticosteroids with the radiopharmaceutical, in both colloidal or particulate radiopharmaceuticals.
7. The importance of combined procedures of saline irrigation with radiopharmaceutical and/or possible corticosteroid injection, for improving patients’ outcome.
8. The value of post treatment full rest (hospitalization?) to prevent extra articular leakage and optimal response.

References

Rhenium radioisotopes for therapeutic radiopharmaceutical development


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The availability of therapeutic radioisotopes at reasonable costs is important for applications in nuclear medicine, oncology and interventional cardiology. Rhenium-186 (Re-186) and rhenium-188 (Re-188) are two reactor-produced radioisotope which are attractive for a variety of therapeutic applications. Rhenium-186 has a half-life of 90 hours and decays with emission of a -particle with a maximum energy of 1.08 MeV and a 135 keV (9%) gamma which permits imaging. In contrast, Re-188 has a much shorter half-life of 16.9 hours and emits a -particle with a much higher energy of 2.12 MeV ($E_{\text{max}}$) and a 155 keV gamma photon (15%) for imaging. While Re-186 is unavailable from a generator system and must be directly produced in a nuclear reactor, Re-188 can also be directly produced in a reactor with high specific activity, but is more conveniently and cost-effectively available as carrier-free sodium perrhenate by saline elution of the alumina-based tungsten-188 (W-188)/Re-188 generator system [1-2]. Since a comprehensive overview of Re-186 and Re-188 therapeutic agents is beyond the scope of this Extended Abstract, the goal is to provide key examples of various agents currently in clinical use and those which are being developed for important clinical applications.

Rhenium-186

One important advantage of using Re-186 is that it can be produced in many nuclear reactors throughout the world, and the 90 hour half-life can often permit distribution to sites distant from the production facility. Which reactors can be used for routine production of Re-186, and the shelf-life of Re-186 inventories, however, depend upon the specific activity requirements. While very high specific activity Re-186, for instance, is required for antibody and peptide radiolabeling [3], preparation of phosphonates for bone pain palliation [4] and use for introversical radiotherapy for inhibition of coronary restenosis after angioplasty is possible with lower specific activity Re-186.

Rhenium-188

A major advantage of the W-188/Re-188 generator is the availability in the clinic of carrier-free Re-188-perrhenate at any time, since elution every 24 hours provides about 50% yields of Re-188. The availability of Re-188 on demand from this high performance generator provides great versatility for development of a range of Re-188-labeled therapeutic agents and
the generators have a long useful shelf-life of > 6 months. Although there are only a few high flux reactors available for production of the W-188 parent [5], the logistics for production and processing of W-188 and the distribution of the W-188/Re-188 can be easily coordinated. Use of inexpensive disposable tandem concentration units [6] is simple and provides very high specific volume solutions of Re-188 (i.e. > 700 mCi/ml from 1 Ci generator). The W-188/Re-188 generator is especially important for providing a reliable source of this versatile therapeutic radioisotope to remote sites, especially in developing regions, which involve long distances and expensive distribution costs.

**Agents for Bone Pain Palliation**

Rhenium-186-\(\text{HEDP}\) is widely used in Europe for the palliative treatment of bone pain from skeletal metastases [4,7]. As alternatives, both Re-188-\(\text{HEDP}\) [8-10] and Re-188(V)-\(\text{DMSA}\) [11] have been developed for bone pain palliation. Patient studies with Re-188-\(\text{HEDP}\) are in progress in Bonn [8] and Dresden [9], Germany, in Montevideo, Uruguay [10], and several other sites, and the Re-188(V)-\(\text{DMSA}\) is being evaluated in patients in Great Britain [11]. Imaging of the 155 keV gamma photon is an advantage which provides an opportunity for estimation of radiation dose to metastatic sites.

**Labeled Antibodies and Peptides for Tumor Therapy**

Various tumor-specific antibodies have also been labeled with Re-186 and Re-188 [3,12]. More recently, somatostatin analogues radiolabeled with therapeutic radioisotopes are of interest for tumor treatment and the RC-160 somatostatin analogue has been directly labeled with Re-188 and evaluated in nude mice having human mammary gland, prostate and small lung cell carcinoma tumors resulting in significant reduction or elimination of the tumors [13]. The extremely short vascular stability of this agent, however, requires the direct tumor or cavity administration.

**Radiation Synovectomy**

An important treatment of inflammatory disease is the use of Re-186-labeled sulfur colloid particles for therapy of rheumatoid arthritis of the synovial joints [14]. Rhenium-186-labeled particles are commercially available in Europe, for example, for this clinical application, but are not yet available in the U.S. Because of expected cost effective on-site preparation in the nuclear pharmacy when required, several groups are also exploring the use of the Re-188-labeled particles for this application [15-16]

**Labeled Particles for Tumor Therapy**

Rhenium-188-labeled particles are also being evaluated for direct tumor injection or administration via the tumor arterial supply. In one study, Re-188-labeled Aminex A27 microspheres (15-20 m) [17] were directly injected into tumors from N1-S1 hepatoma cells in the lobes of the livers of Sprague-Dawley rats. About 80 per cent of the treated rats survived over 60 days after intratumoral injection, while only about 26 per cent of the non-treated rats survived during the same time period. The stability of several other Re-188-labeled microspheres has also been evaluated by incubation with human plasma and by biodistribution studies in rats [18]. The most favorable biodistribution properties were found for the Re-188-\(B-20\) \(\text{HSA}\) microspheres (Mallinkrodt; 15-20 m). The Re-188-labeled sulfur colloid is also simple to prepare [15], with a tight particle size range (86 % = 5 m), with most activity retained in the liver via both intravenous and hepatic artery injection.
Treatment of Non-Malignant Disease

We have also proposed and evaluated Re-188-labeled agents for the use of Re-188 liquid-filled angioplasty balloons inflated at low pressure following coronary angioplasty for the inhibition of coronary restenosis by high dose delivery [19-20]. Angioplasty balloons are filled at low pressure (2-3 atmospheres of inflation pressure) with a solution of Re-188-perrhenate or Re-188-MAG3 following high pressure angioplasty to deliver a dose of 2,500-3,000 rad at 0.5 mm of depth. This application is expected to be important for the inhibition of the hyperplastic component of coronary restenosis. Swine studies have demonstrated the inhibition of restenosis with the Re-188 liquid filled balloon approach after coronary overstretch injury [20] and patient studies are in progress. The use of Re-186-liquid-filled balloons for restenosis therapy is also being evaluated [21].

Acknowledgment

Research at ORNL sponsored by the Office of Biological and Environmental Research (OBER), U.S. Department of Energy (DOE) under contract AC05-960R22464 with Lockheed Martin Energy Research Corporation.

References


Treatment of Bone Pain II
Thursday 21 January 1999 : 14.30 - 15.30
Systemic administration of radiopharmaceuticals is a recognized alternative method for pain treatment in patients with multiple bone metastases. Local field radiotherapy usually solves the pain in single sites lesions, but more frequently the clinical situation involves multiple skeletal lesions and hemibody irradiation has significant toxicity. Long half-life, pure $\beta$ emitters like $^{32}$P and $^{89}$Sr, were followed by shorter half-life radiopharmaceuticals like $^{153}$Sm-EDTMP and $^{186}$Re-HEDP with good clinical results. As a new option $^{188}$Rhenium ($\beta$ energy 2.1 MeV; $\gamma$ energy 155 keV; half-life 16.9 h) can be obtained from a $^{188}$W(tungsten)-$^{188}$Re generator and used for pain treatment in bone metastases as $^{188}$Re-HEDP. Parent nuclide $\beta$ emission decay ($^{188}$W, $t_{1/2} = 69.4$ d) allows a long half-life generator, well adapted for clinical use [1][2]. An HEDP kit for labeling with $^{188}$Re was formulated, controlled and tested in mice, rats and rabbits to establish parameters of biodistribution, dosimetry and image acquisition [3]. A Phase I study was conducted for human administration, determining biodistribution and allowing a dosimetric study in patients [4]. A series of 14 treatments in 12 patients was performed following a protocol that includes a tracer dose followed in 1-2 days by a therapeutic dose, reaching a total dose of $31 \pm 6$ mCi ($1147 \pm 222$ GBq) of $^{188}$Re-HEDP. The patients had pain due to multiple metastases from cancer of the prostate ($n = 6$), breast ($n = 5$) and uterus ($n = 1$) all of them with positive $^{99m}$Tc-MDP scans. All of them underwent bladder catheterization and serial urine collection for a minimum of 6 h and whole body scans at 3 h after tracer and therapeutic dose administration. All of these patients were followed-up by weekly clinical interview and blood cell count for a minimum of 2 months.

More than 50% pain relief was found in 91% of the patients with total relief in 41% of them. One patient did not feel any pain relief and could not decrease former analgesic medication. The rest of the patients were able to decrease in different degrees opiate analgesic intake and in 4 cases they suppressed it completely. Minor analgesic drug intake was decreased in 58% of the cases and 3 patients left all medication. Pain relief started at a mean of 2.1 weeks after dose administration and had a mean duration of 3.7 weeks. A bone uptake of $40 \pm 16\%$ was found for the 12 patients. Using MIRDose3 and a model based on a continuous bladder evacuation and a 50% distribute of radiopharmaceutical between trabecular and cortical bone, a bone marrow absorbed dose of $2.2 \pm 0.8$ mrad/mCi ($5.9 \pm 12.1$ mSv/GBq) and the contribution to total bone marrow of $65 \pm 28$ mrad ($0.176 \pm 0.07$ Sv) were calculated.
Accumulated urine excretion as percent administered dose versus time shows a $40 \pm 16\%$ injected dose is remanent after 24 hours. Mean residence time is $4.7 \pm 1.8$ hours. In a previous work a blood clearance curve showed a three compartment model with transit half life of $0.14 \pm 0.16$ hours for blood in the delayed phase and $0.12 \pm 0.11$ for plasma. Hematological toxicity was found in one patient, whose basal hematic count was low and in whom the dose was performed for humanitarian reasons.

Estimated doses using dynamic model of MIRDOSE3 for different urine elimination parameters showed a low bladder contribution to total absorbed dose, which would enable to avoid the use catheterization during dose administration.

Comparative series [5] and [6] using generator or Irradiation obtained $^{188}$Re, and reporting similar number and pathology patients, tested increasing doses of the radiopharmaceutical with hematological toxicity appearing at higher doses. Maxon et al. performed external dosimetry measures showing low potential radiation exposures to general population. Palmedo et al. found higher marrow toxicity at higher therapeutic doses, having reached up to $120$ mCi in their series.

In conclusion, the use of short lived generator producer $^{188}$Re as a bone seeking agent for pain relief under the form of a phosphonate complex is a promising alternative to long lived $\beta$ emitters Phosphorus and Strontium. $^{32}$P has more metabolic pathways, other then bone, conditioning adverse reactions, and $^{89}$Sr, as a pure $\beta$-emitter does not allow external detection and has a very long half-life. For $^{188}$Re-HEDP, very good quality radionuclide, low carrier amount and low contamination factor with low radionuclidic impurities gives a safe performance. Similar results in pain relief have been observed with a lower bone marrow contribution to total absorbed dose than that reported for the new generation of $^{153}$Sm and $^{186}$Re radiopharmaceuticals. As an advantage, the use of long lived generators makes Re-HEDP a very interesting choice in terms of cost-benefit and availability.

References

Palliative effect of Re 186 HEDP in different cancer patients with bone metastases

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Introduction

The clinical picture of bone metastases is dominated by pain, the loss of mechanical stability. Standard treatment options for bone metastases include external beam radiotherapy and the use of analgesics. Due to large number of lesions in many patients (pts), using of radionuclide therapy with beta emitters may be preferable. Re 186 hydroxyethylidene diphosphonate (Re 186 HEDP) is one of the radiopharmaceuticals suitable for palliative treatment of metastatic bone pain. The aim of this study was to investigate palliative and side effects of Re 186 HEDP in pts with different types of cancer.

Material & method

Thirty one (17 male, 14 female) patients with cancer (10 prostate, 10 breast, 4 rectum, 5 lung, 2 nasopharynx) and bone metastases were included in the study.

Pts were between 39 to 84 year old (mean age 58 ± 5) and cancer history of the pts were between 1 to 4.9 year (mean: 3.6). Including criteria were:

1. At least four bone metastases demonstrated in bone scan,
2. A Karnofsky performance status of maximum 60%,
3. At least 4.0 x 1000 leukocyte and 150 x 100 platelet count,
4. Normal renal functions (30 mmol/Lt serum creatin concentration or less),
5. At least 3 months projected life expectancy.

The pts with either bone marrow suppression were excluded from the study. The pain relief assessed with ECOG and Karnofsky status index. All pts were evaluated with standard evaluation form and the dairy was marked daily for maximum of 10 weeks. A total of 40 standard doses (Re HEDP, Mallinckrodt, Holland) were applicated in, 6 pts received repeated doses (3 dose in 3 pts, 2 dose in 3 pts). Therapy was started with the fixed dose of 1295 MBq of Re 186 HEDP. If necessary it was repeated the same dose at least 3 times in an interval of 10-12 weeks after the other.

Re 186 HEDP standard dose of 1295 MBq was given iv. to the patients with slow infusion. The patients were kept in nuclear medicine department for 6 hours after injection. The next day anterior and posterior whole body scanning was performed. Daily symptomatic response of patients were recorded whereas blood analysis were made weekly for 8 weeks after the therapy. A control Tc 99m MDP scintigraphy was performed approximately 30 days after the therapy.

Results

Response was found as 81.5% in pts with breast and prostate Ca, 75% in pts with rectum Ca, 50% in pts with nasopharynx Ca and 20% in pts with lung Ca. For all pts, response was 67.5%. Palliation period was changed between 6 to 10 weeks. Mean palliation period was 8.1 ± 1.3 weeks. Maximal palliation effect was observed between 3rd and 7th weeks.
Single dose was given in 25 pts. 12 pts with multiple organ metastases and high progress showed low response rate or no answer. The treatment was not repeated in these pts.

3 pts received 3 doses, 3 pts received 2 doses and the treatment repeated in an interval of 8 weeks. The treatment was repeated in pts with high response of the first treatment when pain started again. The rate of response of the repeated dose was slowly lower than the first treatment. The haematological side effects were slightly augmented. The palliation period of the repeated dose was approximately the same as the first treatment.

Flare up phenomenon was observed in four pts, for a mean period of 1 week. Although, 22 pts had cranial metastases, any neurologic complication were not observed in treated pts. Biochemical tests remained in the normal level, except alkaline phosphatase (AP). AP showed a transient decline over 4 weeks. The leukocyte and platelet counts showed slight decrease (10-15 %) at 3-4 weeks and to be normal at 5-7 weeks. Tumor markers had a slight increase of PSA in pts with prostate Ca, no change of CEA and Ca 15-5 in pts with breast Ca and Ca 19-9 in rectum Ca, comparing with before the treatment.

Discussion & conclusion

The response rate for palliation of bone pain in pts with breast, prostate, rectum cancer and was found to be 75%-87.5% which is comparable to that of Sr-89. Response in the pts with lung cancer is not good. We could not clearly explain the reason of the unsuccessful results in those pts. But, pleural invasion and/or hormonal effects may be the cause of continuation of bone pain. Mean palliation period with Re 186 HEDP was 6-10 weeks which is less than with Sr 89. But possibility of repeated application of Re 186 without any serious complication may prolongs the period of palliation. Another advantage of Re 186 HEDP was earlier onset of palliation (1-2 weeks)

It is concluded that Re 186 HEDP is a highly effective agent in the palliation of metastatic bone pain in pts with prostate, breast, rectum cancer, mildly for nasopharynx cancer, but not in lung cancer. On the other hand, Re-186 seems to be a good alternative to Sr-89 because its preferable physical characteristics (as short half life and gamma energy), low side effects, early response and repeated applicability.
Radiochemical studies and pharmacological behaviour of $^{186}$Re complexes of phosphonate ligands

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The direct synthesis of the $\alpha$-aminomethylphosphonic acid have been achieved using orthophosphorus acid, alkylamines and formaldehyde in molar ratios of 4:1:4. The Mannich-type reaction in strong acidic medium (concentrated hydrochloric acid) under reflux, proceeds almost quantitatively [1]. A series of $\alpha$-aminomethyl phosphonic acids have thus been synthesized by varying the diamino unit from 1, 2-diaminoethane in EDTMP (Ligand I) to 1, 3-diaminopropene, 2, 2-dimethyl-1, 3-diaminopropene and 1, 4-diaminobutane to yield the higher homologues PDTMP (Ligand II) DMPDTPM (Ligand III) and BDTMP (Ligand IV). All the ligands were crystallized to solid derivatives and subsequently characterized using $^1$H-NMR spectroscopy.

$^{186}$Re as ammonium perrhenate was obtained by irradiating natural rhenium metal powder in the reactor and further processing as reported by us earlier [2]. 100 µg (0.5 µM) of $^{186}$Re was used for complexation studies. The complexation reactions were carried out in acidic medium (pH 2) by reacting the ligands with rhenium in the presence of stannous chloride as the reducing agent. The final reaction volume was made to 1 mL with saline. The reaction was carried out in boiling water bath for 30 minutes. The complexes prepared were characterized by paper chromatography in acetone and saline as solvent systems. In paper chromatography using saline as solvent, the complexes showed movement with the solvent front while in acetone, the complexes remained at the point of spotting. The complexes were negatively charged as the migration was observed towards anode in paper electrophoresis. The reaction conditions, such as reagent concentrations, pH, time and temperature were optimized to get maximum complexation yield. All the ligands showed complexation with $^{186}$Re in highly acidic medium (pH 2) and the complexation yields were >90%. The complexation yield decrease with increase in pH. In case of the complex of ligand I and III, increase in yield was observed at pH 7. Optimum amount of stannous chloride required for complexation was 1 mg and of the ligands required were 30 mg for ligand I, II and III and 50 mg in case of ligand IV. At lower concentration of ligand, turbidity appeared in the reaction mixture resulting in the formation of colloidal Re. In the case of the complexes of ligands I, II and III it was essential to heat the reaction mixture in a boiling water bath for 30 minutes to get maximum complexation yield. In the case of the complex of ligand IV, the reaction was instantaneous. However, it was observed that stability of the complex was poor when the complex was prepared at room temperature. Stability was also dependent on the time for which the complex was heated in a boiling water bath. It was observed that the complex of ligand I was stable at room
temperature for one week. Complexes of ligands II and III were stable only when stored at 4°C for the same period. Stability of the complex of ligand IV was less even at 4°C.

Biodistribution studies of the complexes were carried out in male Wistar rats weighing 150-200 g. 0.2 mL of the complex (7.4 MBq) was injected intravenously in rats. Rats were sacrificed after 3h, 24h and 48h. Organs and tissues were excised and counted in sodium iodide scintillation detector. Blood, bone and muscle weight were taken as 7%, 6.5% and 40% of the body weight respectively for calculation. It was observed that activity was cleared faster from blood. Bone uptake observed was in the range of 14-32% in case of complexes of all the ligands and the activity in bone was retained for 48h. Maximum bone uptake was with complex of ligand IV (32% 24h p.i.). Residual activity in other organs was minimum in case of complex of ligand III with 80% excretion after 3h p.i. In case of the complex of ligand II, kidney retention was more (15% at 48h p.i.) while with the complex of ligand IV retention in liver was more. Results of the biodistribution studies of the complex of ligand I and III are given in Table 1.

Table 1. Results of the biodistribution studies of the complexes of ligand I and ligand III

<table>
<thead>
<tr>
<th>Product</th>
<th>Time</th>
<th>Blood</th>
<th>Bone</th>
<th>Liver</th>
<th>Kidney</th>
<th>GIT</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{186}$Re-EDTMP (Ligand I)</td>
<td>3 h</td>
<td>0.8 (0.4)</td>
<td>14 (2.6)</td>
<td>0.5 (0.1)</td>
<td>1.2 (0.6)</td>
<td>2.3 (1)</td>
<td>80 (1.8)</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>0.5 (0.1)</td>
<td>16 (0.7)</td>
<td>0.4 (0.1)</td>
<td>0.9 (0.4)</td>
<td>2.2 (0.5)</td>
<td>82 (8.7)</td>
</tr>
<tr>
<td></td>
<td>48 h</td>
<td>0.5 (0.2)</td>
<td>17 (2.0)</td>
<td>0.8 (0.1)</td>
<td>3.8 (1.3)</td>
<td>4.1 (1)</td>
<td>80 (4.6)</td>
</tr>
<tr>
<td>$^{186}$Re-DMPDTMP (Ligand III)</td>
<td>3 h</td>
<td>0.4 (0.1)</td>
<td>21 (3)</td>
<td>0.3 (0.1)</td>
<td>1.0 (0.1)</td>
<td>0.8 (0.2)</td>
<td>75 (4.0)</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>0.1 (0)</td>
<td>16 (4)</td>
<td>0.2 (0.1)</td>
<td>0.5 (0.1)</td>
<td>1.0 (0.1)</td>
<td>80 (7.8)</td>
</tr>
<tr>
<td></td>
<td>48 h</td>
<td>0.1 (0)</td>
<td>16 (2)</td>
<td>0.2 (0.1)</td>
<td>0.5 (0.1)</td>
<td>0.7 (0.2)</td>
<td>80 (6.2)</td>
</tr>
</tbody>
</table>

Values reported are % activity per organ with SD n = 3

References

Sm-153 EDTMP for palliation of pain from osseous metastases: Preparation and biodistribution studies

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The lung, breast and prostate cancers are the most frequent in our country. These cancers generally metastasize to the skeleton and a significant number of patients experience bone pain. The use of therapeutic radiopharmaceuticals which localize at metastatic sites has been found to be an effective new method for the treatment of pain and has many advantages over the use of analgesics and external radiation. Among these radiopharmaceuticals, Samarium-153 EDTMP is the better agent thanks its short half-life, a high bone uptake and a rapid excretion from the body.

In this paper, we report results of Sm-153 EDTMP preparation, its uptake by shell of eggs as osseous model and its biodistribution in small animals.

**Sm-153 EDTMP preparation**

Sm-153 is produced by irradiation of Sm$_2$O$_3$ (enriched at 98.7%, provided by the IAEA), sealed in a quartz ampoule at a thermal neutron flux of $10^{13}$ n/cm$^2$ s in the Research Reactor NUR during 54 h (discontinuous irradiation). Sm-153 activity is recovered from irradiated target in hot diluted hydrochloric acid. Activity and radionucleidic purity were determined by gamma spectroscopy by counting an aliquot of obtained solution on HPGe detector. Gamma spectrum of Sm-153 is shown in fig. 1. The spectrum obtained with lead shielding contains the other characteristic peaks (463.3 keV, 531.0 keV, 608.9 keV). Specific activity of 50 mCi/mg of a pure Sm-153 chloride was easily obtained. The solution of Sm-153 chloride is used without further purification.

![Gamma-spectrum of Samarium-153.](image)

*Left, without shielding; right, with lead shielding.*
Sm-153 EDTMP is prepared by adding Sm-153 chloride to a solution of EDTMP. Large quantities of pure EDTMP were previously synthesized from phosphorous acid and ethylenediamine using the Mannich-type reaction [1]. Optimization of labeling conditions was performed. The radiochemical purity, assayed by ITLC SG chromatography system was higher than 98%. Sm-153 EDTMP was stable more than 5 days.

**Biodistribution studies**

In-vitro uptake of Sm-153 EDTMP by shell of eggs as osseous model was studied to confirm mechanism of its localization as it was previously done for Tc-99m diphosphonates [2]. In-vivo biodistribution studies were performed in mice and rats. Scintiphotos of rats and eggs, imaged with Sm-153 EDTMP are shown in Fig. 2.

*Fig. 2. Scintiphotos of hen eggs (left) and rats (right) imaged with Sm-153 EDTMP.*

It was noted a high fixation of Sm-153 EDTMP by shell of eggs as for Tc-99m diphosphonates. This confirm the high affinity of phosphonate complexes for the mineral bone matrix and particularly for the calcium carbonate crystals in the case of shell of eggs.

Biodistribution studies in mice and rats showed high selective skeletal uptake, rapid blood clearance and high bone-to-soft tissue ratios. No specific fixation in non-osseous tissues and organes was found. Sm-153 EDTMP is eliminated from the body principally by renal excretion.

It can be concluded that the performance of the therapeutic radiopharmaceutical Sm-153 EDTMP in mice and rats was very satisfactory. It is planned to be further investigated by additional biological and clinical experimentation.

**References**

Radiochemical and biological studies, including in non-human primates, towards indigenous development of $^{153}$Sm-EDTMP


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Introduction

The combination of ease of formulation and superior biological features of $^{153}$Sm-EDTMP in terms of safety and efficacy for metastatic bone pain palliation, together with the prospect of relatively reasonable cost, has prompted extensive efforts by many groups world over to standardise methods for its preparation and evaluation [1,2]. Our efforts have been directed towards establishing feasibility of use of inexpensive and freely available natural samarium oxide targets by neutron activation in medium flux reactors in our country. Towards this aim, we have formulated a number of batches of $^{153}$Sm-EDTMP and evaluated the product for its ease of production, purity, stability, safety and efficacy of bone uptake and excretory pattern in test animals, including in monkeys.

Results and discussion

5-10 mg of natural samarium oxide was irradiated at a neutron flux of 6-8 x $10^{13}$ n. cm$^{-2}$. s$^{-1}$ in the Dhruva reactor for about seven days and dissolved in hydrochloric acid. Specific activity of 500-700 mCi $^{153}$Sm per mg Sm (at EOB) and radioactive concentration of over 400 mCi/ml was obtained. Complexation of the samarium with a gift sample of EDTMP as well as an in-house synthesised product was carried out under conditions previously standardised by us [3] at a ligand to metal mole ratio of 20 - 40 : 1. Formulations at radioactive concentration of 10-50 mCi/ml were prepared and the radiochemical purity and stability evaluated by paper chromatography. Stability of $^{153}$Sm-EDTMP in serum was also followed. The product even when stored at room temperature (RT) was found to be stable for 8 days at RC purity >98% for formulations at 10-12 mCi/ml radioactive concentration; but, as expected, formulations at much higher radioactive concentration were found to be stable for 5 days only (at RT) at a RC purity of upto 90%. High resolution γ spectrometry studies using HPGe detector revealed radio-europium contamination ($^{154/155/156}$Eu). At 2 days from EOB each mCi of $^{153}$Sm contained typically 0.013 uCi $^{154}$Eu, 0.15 uCi $^{155}$Eu & 1.5 uCi $^{156}$Eu. These values are consistent with our earlier reports in literature [3,4]. Improvement of radionuclidic purity (but at the cost of reduced yield) could be achieved by radiochemical purification [4], but is not deemed essential in the context of therapeutic application envisaged and known similarity in biological behaviour of Sm and Eu chelate of phosphonates. Further, mice administered EDTMP doses of upto 4 mg / animal exhibited no untoward toxic symptoms giving a safety factor of >300 at expected adult doses. In other words, samarium content and radionuclidic purity aspects need not be deterrent factors for the use of natural samarium target for the manufacture of $^{153}$Sm-EDTMP.

The bio-distribution studies in rats showed 2.5 to 3.5 % injected dose in femurs 1h p.i. for all samples and even at 5 days post formulation. Anaesthetised monkeys were administered 0.5-1 mCi 153Sm per kg through a leg vein and images recorded with a gamma camera (Siemens, Orbiter) upto 116 hours p.i. Fig.1 shows the good retention in skeleton throughout the period of study and no significant retention in any other tissues. Comparative studies using enriched 152Sm target and also a commercial sample of 153Sm-EDTMP are underway. These
results have thus established satisfactory feasibility for production, adequate safety and biolocalisation of the indigenous product so as to warrant clinical trials in patients.

Fig. 1. Gamma camera images of a monkey injected with $^{153}$Sm-EDTMP

Acknowledgments

The authors thank Dr. S. Gangadharan, Chief Executive, BRIT for encouragement. The studies in non-human primates form a part of a BRNS, DAE Project of CMC&H, Vellore, India.

References

Efficacy and toxicity of 153 samarium-EDTMP locally produced in the treatment of painful skeletal metastases


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2CGM Nuclear, Santiago, CHILE

This project is being carried out in conjunction with the IAEA. The goal is to determine the efficacy and toxicity of $^{153}$Sm-EDTMP. The administered dose for the studied patients were divided in two groups: Group I: 0.5 mCi/kg and Group II: 1 mCi/kg body weight. Written consent was obtained. $^{153}$Sm-EDTMP was obtained from enriched $^{152}$Sm irradiated at a 5 MW research reactor and labelled with EDTMP at a molar ratio of 15:1 and pH 7.5. Biodistribution, autoradiography, and radiochemical purity test were done for evaluation. Blood test and follow up were done during 16 weeks.

**Results**

<table>
<thead>
<tr>
<th></th>
<th>GROUP I</th>
<th>GROUP II</th>
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<tbody>
<tr>
<td></td>
<td>$\bar{x}$</td>
<td>range</td>
</tr>
<tr>
<td>AGE</td>
<td>64.9</td>
<td>42 - 83</td>
</tr>
<tr>
<td>WEIGHT (kg)</td>
<td>67.6</td>
<td>43 - 100</td>
</tr>
<tr>
<td>DOSIS (mCi)</td>
<td>33.6</td>
<td>20 - 50</td>
</tr>
<tr>
<td>CREATININE</td>
<td>0.96</td>
<td>0.7 - 1.38</td>
</tr>
<tr>
<td>SEX</td>
<td>12 M</td>
<td>4 F</td>
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</tbody>
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**Type of cancer**

<p>| | |</p>
<table>
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<tbody>
<tr>
<td>Prostate</td>
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<tr>
<td>Breast</td>
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<tr>
<td>Adenoca.</td>
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</tr>
<tr>
<td>Lung</td>
<td>1</td>
</tr>
<tr>
<td>Endometrium</td>
<td>1</td>
</tr>
<tr>
<td>Colon</td>
<td>1</td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
</tbody>
</table>

**Response**

<table>
<thead>
<tr>
<th></th>
<th>GROUP I</th>
<th>GROUP II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>No change</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Slight relief</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Moderate relief</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Complete relief</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>
Medullary suppression (percentage of drop related to baseline)

<table>
<thead>
<tr>
<th></th>
<th>GROUP I</th>
<th>GROUP II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>range</td>
</tr>
<tr>
<td>WBC</td>
<td>29.2</td>
<td>11 - 60</td>
</tr>
<tr>
<td>granulocytes</td>
<td>31.3</td>
<td>8 - 70</td>
</tr>
<tr>
<td>platelets</td>
<td>42.6</td>
<td>8 - 80</td>
</tr>
</tbody>
</table>

Based in our preliminary results it seems that the efficacy is not dependent on dosis but the toxicity is related to the activity injected.

We believe that $^{153}$Sm-EDTMP is a very good option to treat metastatic bone pain in those countries where a reactor is available and at a very affordable cost.

References

Random comparison study of the clinical response to 153 Sm-EDTMP 1.0 mCi/kg and 1.5 mCi/kg

Zhongyun Pan and Shaoli Zhu
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The usual dose of 153Sm-EDTMP used in the treatment of metastasis bone pain is 1.0 mCi/kg. But the efficacy of this dose is not much satisfying. A comparison study of the clinical response to 1.0 mCi/kg and 1.5 mCi/kg is being carried out in hopes of promoting efficacy without increasing toxicity. The total number of patient enrolled this study is sixty. So far, only 29 patients were observed completely. Although it is impossible to reach reasonable conclusion based on so limited observation, we report the preliminary results as follow.

Subjects

Seventeen patients received 153Sm-EDTMP 1.0 mCi/kg (group I) and twelve received 1.5 mCi/kg (group II), randomly. All the patients with multiple skeletal metastasis suffer from moderate or marked bone pain with WBC > 3.5 x 10^9/L and PLT > 80 x 10^9/L.

Methods

After receiving dose, patients were kept in close follow-up weekly with blood sampling, physician visiting and patient self-filling-in diary collecting. After study was completed, patient’s overall condition was assessed based in the changes of pain score, Karnofsky performance scale and analgesic consumption. The overall condition were graded into no change even worse (0), slight relief (I), significant relief including moderate relief and marked relief (II) and complete relief (III). Only II and III were considered as effectiveness for pain relief. Haematology toxicity was evaluated based on the nadir counts of WBC and PLT.

Results

1. Pain relief (Table 1)

In group I, 8 patients had pain released, analgesic reduced and general condition improved significantly, and one patient had pain released completely. Therefore the effectiveness rate was 52.9% (9/17).

In group II, the effectiveness rate was 66.7% (8/12).

Table 1. 153Sm-EDTMP Efficacy in pain relief

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>Effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>17</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>1</td>
<td>9 (52.9%)</td>
</tr>
<tr>
<td>II</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>8 (66.7%)</td>
</tr>
</tbody>
</table>

2. Haematology Toxicity (Table 2)

In group II, The sum of WBC toxicity grade II and III was 6/12, higher than that of group I (4/17). On the contrary, the sum of PLT toxicity grade II and III in group II was 4/12, much less than that of group I (10/17). The nadir time of WBC and PLT of both groups were almost the same (around 4 wks). None of life-threatening haematology toxicity (grade IV or more) was noticed.
Table 2. 153Sm-EDTMP Haematology Toxicity

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>nadir time</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>nadir time</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>17</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>3.8 wks</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td>3.8 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2~6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2~6)</td>
</tr>
<tr>
<td>II</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>4.1 wks</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>4.3 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2~5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2~6)</td>
</tr>
</tbody>
</table>

WBC toxicity grade: 0 (≥ 4 x 10^9/L), I (3 ~ 3.9), II (2 ~ 2.9), III (1 ~ 1.9)

PET toxicity grade: 0 (≥ 100 x 10^9/L), I (75 ~ 99), II (50 ~ 74), III (25 ~ 49)

Preliminary impression

The efficacy of bone pain relief of 153Sm-EDTMP 1.5 mCi/kg seems higher than that of 153Sm-EDTMP 1.0 mCi/kg. At the same time, higher dose did not induce more severe heamatology toxicity. These results are encouraging. Of course, the final reasonable conclusion would not be reached until the whole study completed.
Radioimmunotherapy: Opportunities, obstacles and challenges, with special reference to developing countries

Divgi C.

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Preparation and evaluation of various $^{32}$P sources for intravascular brachytherapy

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1 The Niewodniczanski Institute of Nuclear Physics, Radzikowskiego 152, 31-342 Kraków
2 The Silesian Medical Academy, II Dept. Cardiology, Skłodowskiej-Curie 10, 41-800 Zabrze, POLAND

Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is a powerful means for treatment of coronary disease, but still not free from a relatively high percent of restenoses which may lead to repetitive treatment. The search for ways of preventing this effect revealed that radiation doses of 10-30 Gy play a positive role in remodelling of the arterial wall, which in mid-nineties initiated the practice of post-PTCA intravascular brachytherapy (IVBT). Among suggested IVBT sources ($^{90}$Y, $^{32}$P and $^{192}$Ir [1, pp. 181, 207, 296]) $^{32}$P has advantages such as favourable half-life (T½ 14.3 d), decay by pure $\beta$ emission and short range of the emitted particles. [1, p. 323].

Physical form of the source determines the treatment fractionation and technique (high or low dose rate). As a preliminary study to catheter-based or stent-based IVBT techniques we have been evaluating several methods of preparation of $^{32}$P sources, taking into account properties of stent or thrust wire materials like: pure titanium, Ti-Ni alloy and stainless steel.

Methods of preparation of solid sources

a) Implantation of phosphorus onto metallic surfaces

Beams of ions are very suitable for doping thin surface layers of solids by stable or radioactive isotopes, or for creation hard complex coating layers with very good adhesion.

An easy way of source preparation is implantation of stable $^{31}$P into purest Ti substrate. The implanted $^{31}$P can be later activated with thermal neutrons to $^{32}$P, without much risk of activating the supporting material. In the case of stainless steel or titanium alloys, ion beam modification of the surfaces requires direct implantation of radioactive $^{32}$P. Otherwise, contrary to titanium of highest purity, thermal neutron bombardment would activate unwanted longlived gamma-emitting nuclides in these materials.

Initially, we were implanting pure stable phosphorus onto solid surfaces. By the dual beam IBAD methods another set of metallic surfaces was covered by thin carbon layer doped by phosphorus. The depth distribution of $^{31}$P in Ti and in C was investigated by proton beams (RBS and PIXE methods).

Our dual beam 75 kV ion implanter, used either for implantation or for the IBAD technique was described in detail in Ref[3]. Phosphorus was implanted with an energy of 25 keV. The currents of the $^{31}$P beams were 0.05 - 0.2 $\mu$A.

b) Chemical conversion coatings

The alternative for pure titanium stent (which, to our knowledge, has not been described in the literature) is the Nitinol or the stainless steel one (Palmaz Schatz or much cheaper of our own construction [4]). To avoid either production of long-lived contaminants in the alloy
material or radioactive contamination of our ion implanter, we tried a wet method of fixing $^{32}\text{P}$ on the stainless steel surface (SS). Preliminary experiments were performed with $^{31}\text{P}$ phosphates on highly polished 3 mm x 5 mm x 10 mm plates of austenitic chromium-nickel steel (AISI 316L), preprocessed as in Ref.[2]. By immersing the plates in hot acidic phosphate solutions we obtained thin conversion coatings on whose quality we are still working. The deposition process was observed by measuring the electrochemical potential relative to the standard calomel electrode. Time necessary for reaching the chemical equilibrium was about 60 minutes. The deposition of $^{31}\text{P}$ on the SS subrace was also investigated by RBS and PLXE methods.

Dosimetric considerations

The main problems in dosimetry of $^{32}\text{P}$ radiation are high dose-rate gradients within a volume of a few millimetres. To obtain a good spatial resolution we used miniature thermoluminescent LiF detectors specially developed for that purpose in our laboratory. They have form of pellets with diameter of 2 mm and effective thickness of about 0.1 mm. Measurements were performed within a PMMA phantom (modified version of that by Popovski et al [1, p. 336] enabling placement of detectors at various distances from a source.

Conclusions

Ionic methods are recommendable for deposition of phosphorus into the metal surface layer. Their advantage is that they produce very hard, friction- and chemically resistant surfaces which can be considered as sealed sources. Its limitation is the risk of contamination of our multipurpose apparatus with radioactive $^{32}\text{P}$. Neutron activation of the $^{31}\text{P}$ implanted stents or thrust wires is recommendable only for those from purest Ti but not for the stainless steel or Nitinol (Ni-Ti) ones because of the activation of long-lived gamma emitting nuclides in these alloys.

The technique of thin [$^{32}\text{P}$] conversion coatings on the stainless steel still requires experiments on their mechanical properties and the chemical resistance.

Acknowledgments

This work was partially financed by the Polish Committe of Scientific Research, grant no 4 P05B 132 14. One of us (BP) is indebted to the Nucletron Company for the kind gift of the monograph quoted in Ref. 1. Technical assistance of Mr M. Bartyzel and Mr J. Dybet is gratefully acknowledged.

References

Use of TLD in dosimetry of beta emitters for therapy

Nuclear Medicine & RIA Unit, S.N. Medical College, Agra, INDIA

Quantification of radiation absorbed dose in radioimmunotargeting is essential to understand the dose response relationship, the optimum activity of the selected radionuclide to produce the desired effect i.e. cell kill and up to some extent the amount of antibody required. Absorbed dose estimates are usually based on the in-vivo quantitation of radioactivity in the biological system (using MIRD formulation) for which data are obtained using radionuclide imaging techniques including planar scintigraphy, SPECT and PET. However, the imaging of small animals is limited by the resolution of the camera system and therefore inadequacy in the data provided. It is therefore appropriate to supplement the data with the small TLDs incorporated in the various organs/tumour. TLDs will record the profile of the time activity curve as absorbed dose. It will record dose from its own plane as well as from the surrounding planes with in the range of the particulate radiation (cross fire from β emitters) as well as gamma radiation.

The present study has been performed with $^{199}$Au, a promising candidate radionuclide with effective β emissions 0.30 Mev (70%), 0.25 Mev (24%) and 0.46 Mev (6%) and useful gamma radiation for localization studies. However, inspite of good in-vitro labelling of immunoglobulins by $^{199}$Au, the use of $^{199}$Au is limited by the in-vivo behavior of the labelled gold in the biological system. Efforts to improve the stability of the linkage of $^{199}$Au with the antibody includes the use of agents such as cyclic DTPA, which was used for linkage of other radiometals to antibodies as well as phosphines which have been reported useful in linking gold to peptides. The comparison of the biodistribution and dosimetry of such gold labelled antibodies with that of native gold is also of relevance.

So far as use of TLDs for such quantification is concerned, the calibration of such TLDs with β emitters in physical models is an essential step. This paper describes the use of TLDs for dosimetry with gold in physical phantoms as well as the initial data obtained with animal experiments.

We have modified Anderson’s technique to label $^{199}$Au with proteins. 200 UL of $^{199}$Au received as Auric acid in Hydrochloride acid solution (828 MBq in 7 ml, carrier free) was pH adjusted to 4.5 using 0.5 M NaOH added drop by drop (Anderson described citrate buffer which we observed to give a precipitate with metallic gold). 50 UL of Monoclonal antibody M3 (an anticytokeratin 18 antibody kindly supplied by Bjorklund of the Swedish Cancer Council/ Beki Diagnostic) at a concentration of 5.2 mg/ml in 0.5 M PBS, pH 7.4 was incubated for three hours with above radiogold at room temperature (18°C or below). The reaction mixture was purified by PD-10 column. The paper chromatography has confirmed very good in-vitro labelling.

Nude mice (n=6) having breast carcinoma xenograft implanted on left shoulder region were injected intravenously with $^{199}$Au labelled specific antibody (M3) and Non specific antibody (HlgG). The miniature rod shaped LiF TLDs (TLD-700, 1 mm x 6 mm) were implanted into the tumour bearing nude mice. Few TLDs were pasted externally on different organs which will accumulate gamma contribution at that point. TLD implanted in the tumour however will accumulate dose from both β and γ radiation. Table 1 summarizes the preliminary absorbed dose data obtained at 48 hrs for various organs/tumour (fig-1).
We have also investigated the dose fall off for $^{199}$Au in paraffin phantoms using TLDs. Mini TLDs placed at known distances (comparable to different organ distances in animal models) in the paraffin phantom were exposed to 5.5 MBq of gold for different time intervals (fig-2).

In order to investigate the validity of TLD measurements of β emitters, we also examined the correlation of the densitometry of spots on autoradiographic film induced by β emitter sources, using a Miniscan scanning densitometer and examined their correlation with TLD measurements. These data which are under analysis will be discussed.

It appears that TLD can be utilized in physical phantom models for β dosimetry but there are certain limitations on the interpretation of data particularly in relation to linearity of data. Extreme precision in implantation and localization of the TLDs and of the dose sources may improve the response profile. The comparative measurements of TLD measurements and computer estimates based on distribution data and biodosimetry will be discussed.

**Table 1. Biodistribution of $^{199}$Au labelled HigG & monoclonal antibody M3 in tumour bearing mice (n=6).**

<table>
<thead>
<tr>
<th>SR.NO.</th>
<th>ORGAN</th>
<th>HigG LABELLED</th>
<th>M3 LABELLED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Liver</td>
<td>5.33</td>
<td>0.969</td>
</tr>
<tr>
<td>2.</td>
<td>Kidney</td>
<td>3.09</td>
<td>0.989</td>
</tr>
<tr>
<td>3.</td>
<td>Heart</td>
<td>1.04</td>
<td>0.076</td>
</tr>
<tr>
<td>4.</td>
<td>Muscle</td>
<td>0.18</td>
<td>0.034</td>
</tr>
<tr>
<td>5.</td>
<td>Tumour</td>
<td>0.95</td>
<td>0.041</td>
</tr>
</tbody>
</table>

**Fig. 1.**
Fig. 2.

VARIATION OF DOSE WITH DISTANCE IN PARAFFIN PHANTOM

DISTANCE IN CMS

DOSE IN CGY

24 hrs
48 hrs
96 hrs
144 hrs

Fig. 2.
Tumor geometry, especially its size, is an important consideration in the selection of an appropriate therapeutic radionuclide. The commonly used radionuclides for targeted therapy such as $^{131}$I and $^{90}$Y emit β-particles the mean range in tissue of which is several millimeters. Alpha particles on the other hand, would traverse only a few cells. Absorbed fraction ratio for $^{211}$At α-particles compared with $^{90}$Y β-particles increases from 9:1 for 1-mm diameter tumors to 33:1 for 0.2 mm tumors [1]. Thus targeted alpha particle therapy could be ideally suited for micrometastases, tumors of circulation such as lymphoma and compartmental-grown tumors such as cystic brain tumors, ovarian cancer and neoplastic meningitis. In addition to their range, α-particles have several other radiobiological advantages such as high linear energy transfer (LET) and relative biological effectiveness (RBE), marginal dependence on dose rate, and an oxygen enhancement ratio of close to unity. Although more than 100 α-particle emitting radionuclides exist, only $^{212}$Bi, $^{213}$Bi and $^{211}$At has received serious attention. Astatine-$^{211}$ decays by a double branched pathway resulting in one alpha particle per disintegration having an average energy of 6.8 MeV and 55-70 μm range. The LET of $^{211}$At α-particles is about 100 keV/μm at which maximum RBE occurs. Being a halogen, more often than not, radiiodination chemistry is adaptable for astatination.

Combining the tumor cell specificity of monoclonal antibodies (mAbs) with α-particle-emitting radionuclides is an area which has received serious consideration in targeted therapy. For the astatination of mAbs, $N$-succinimidyl 3-[$^{211}$At]astatobenzoate (SAB) was prepared by the astatination of a tin precursor in excellent yields. Monoclonal antibodies could be astatinated under very mild conditions in excellent yields and specific activities. The resultant astatinated mAbs retained affinity and immunoreactivity and were considerably stable in vivo. Paired-label tissue distribution of the chimeric mAb 81C6 labeled with SAB and that labeled with $N$-succinimidyl 3-[$^{131}$I]iodobenzoate (SIB) was performed in athymic mice bearing D54-MG glioma xenografts. Except in stomach, the uptake of astatine and iodine in normal tissues was similar. The tumor uptake of astatine increased from about 5% ID/g at 0.5 h to about 20% ID/g at 16 h and remained constant thereafter (Fig. 1). Up to 16 h the tumor uptake of both $^{131}$I and $^{211}$At was similar.

Therapy experiments were carried out using the astatinated murine 81C6. Athymic rats with TE-671 rhabdomyosarcoma cell neoplastic meningitis were treated with saline, 12 μCi of astatinated nonspecific mAb, 12 and 18 μCi of $[^{211}$At]-labeled 81C6. Although, compared with saline treatment, there was a 33% (32 vs 23.5) increase in the median survival for control mAb, the difference was not statistically significant. In contrast, treatment with same amount of $[^{211}$At]-labeled 81C6 increased median survival by 113% which was significant compared to both saline and control. With 18 μCi of $[^{211}$At]-labeled 81C6, the median survival was 84 days, a 357% survival prolongation. In comparison, even with 300 μCi of $^{131}$I-labeled fragment of another mAb, Mel-14 in this model only 12% survival prolongation was noticed. Thus, the therapeutic effects of $[^{211}$At]-labeled 81C6 is specific and is better to other modalities in this model.
Another area where the superior therapeutic properties of $^{211}$At can be exploited is in the development of astatinated 5-iododeoxyuridine (I UdR) analogues. When labeled with the Auger-emitting nuclides $^{125}$I and $^{123}$I, the thymidine analogue IUdR was found to be extremely cytotoxic to cells undergoing DNA synthesis. However, due to the very short ranges of these particles, cells not in the S-phase are not subjected to the cytotoxic effects of labeled IUdR. In addition to α-particles, astatine decay is associated with very short range (92 nm) recoil nuclei of high LET. It was hypothesized that an astatinated IUdR analogue may be lethal not only to cells undergoing DNA synthesis but those in non-S-phase due to bystander killing. To investigate this, 5-$^{211}$Atastatodeoxyuridine (AUdR) was synthesized.

![Fig. 1. Paired-label tumor uptake of chimeric 81C6 labeled with $^{131}$I SIB and $^{211}$At SAB in athymic mice bearing D-54 MG glioma xenografts](image)

Cell uptake and DNA-incorporation studies were performed using D-247 MG glioma cells to determine whether AUdR, like IUdR, is a good analogue of thymidine. From a paired-label study using IUdR labeled with $^{131}$I and AUdR, it was shown that the uptake of both tracers was similar, increased linearly with activity concentration and was competitively inhibited by unlabeled IUdR. At an activity concentration of 200 nCi/ml, about 50% of total cell-associated activity was in DNA fraction for both tracers.

Clonogenic survival assay using D-247 MG cells gave a $D_0$ of 350 nCi/ml for AUdR corresponding to less than 1-2 $^{211}$At bound per cell. The $D_0$ for astatide was about 650 nCi/ml. The incubation time for these assay was 20 h during which period 85% of astatine should have decayed. Thus, there should not be much difference in the cytotoxicity of astatide and AUdR. We speculate that the higher toxicity of AUdR may be in part related to the radiative emissions of subcellular range as a result of DNA incorporation of AUdR. When the cytotoxicity of AUdR and $^{125}$I IUdR for D-247 cells was compared, AUdR exhibited more efficient and effective cell killing.

Clinical trials using $^{211}$At-labeled 81C6 are under way for the treatment of CNS tumors. The outcome will indicate the potential usefulness of astatinated mAbs and other agents for the therapy of otherwise untreatable neoplasms.

References

Microdosimetry of astatine-211 and comparison with that of iodine-125

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Astatine-211 as an alpha and Auger emitter radionuclide has an extremely high potential application in cancer therapy, particularly, in molecular radiotherapy. As is known well, the radionuclides which emit short range and high LET radiations such as alpha and/or Auger electrons should be incorporated into the nucleus of cancer cells for resulting high radiotoxic effectiveness. Especially, it is experimentally observed by several authors that high radiotoxicity of Iodine-125 as an effective Auger emitter was observed when it was incorporated into the structure of DNA or found very close to it. This means that the dose distribution within the cell nucleus at the microscopic scale is very important for comparison of real differences between the radiotoxic effectiveness of different radionuclides. It is also important to outline that the microscopic dose calculation methods should consider the real cell nucleus composition. For this reason, such a calculation method should use the cell nucleus models having practically equal elemental composition. In the literature, the water models are generally used for these calculations. In reality, the cell nucleus differs from water in the lower oxygen content, which is replaced principally by carbon. In this context, Ün ak [1] recently developed a dose calculation program of Auger electrons of Iodine-125 within the cell nucleus (code UNAKNUC). In this study, the same program has been adapted to the Auger electrons and alpha particles emitted by Astatine-211,

According to the data given by Stepanek et al. [2], 6.3 Auger electrons and 1 alpha particle are emitted by Astatine-211 per a single decay. In the reality two different particles with intensities of 0.418 and 0.582, are emitted by Astatine-211 and its very short half-lived daughter radionuclide Polonium-211, respectively. An Auger electron spectrum of Astatine-211 has been also given by the same authors. In this study, the microdosimetric calculations was initiated from the spectrum given by Stepanek et al.

The results obtained can be summarized as follows:

1) The total energy absorption by a cell nucleus having a radius of 4 μm from Auger electrons and alpha particles emitted by an Astatine-211 radionuclide placed at the center of the cell nucleus was found as to be about 51.2 keV. The similar energy absorption from Auger electrons of Iodine-125 was earlier calculated by Ün ak as to be about 10.687 keV.

2) At the DNA scale, i.e. in a central sphere within the cell nucleus having a radius of 10 nm, the total energy absorption were found 0.558 keV for Astatine-211, and this was about 0.777 keV for Iodine-125.

3) For an activity of about 0.00209 Bq Astatine-211, which corresponds 78 radionuclide randomly distributed within the cell nucleus results 7 decays during the 1st hour, and the total energy absorption was calculated as to be 134.9 keV, 0.074 Gy, 457.6 keV/ng. The corresponding values are 47.4 keV, 0.026 Gy, 160.5 keV/ng for Iodine-125, respectively.

4) The dose absorption by the cell nucleus as a function of decay time of Astatine-211 and Iodine-125 for the same activity values during the 1st 24 h is shown in the following figure.
Initial activities of $^{211}$At and $^{124}$I : 0.00209 Bq

References


Dosimetric aspects on radioimmunotherapy using the alpha-particle emitter astatine-211

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With an increasing interest in using alpha-particle emitters for radioimmunotherapy (RIT), a correct dosimetry for this application becomes important. Both the number of alpha-particle traversals through the cell nucleus, as well as the mean absorbed dose has been related to the biological effect of astatine-211 [1]. The aim of this study is to show how the expected biological effect as a function of these two parameters differ for two irradiation geometries of importance for radionuclide therapy, i.e. i) homogeneous distribution of the radionuclide surrounding a cell ("free 211At"), and ii) the radionuclide bound to the cell surface ("bound 211At").

A Monte-Carlo program was used for simulating the decay of 211At, and then register the alpha-particles chord lengths through, and energy deposition to a cell nucleus. This was done for "free" and "bound" radionuclide distribution. The difference in both chord length and energy deposition distribution for the two geometries was then used for theoretical cell survival curves.

The distribution of energy deposition per event to a cell nucleus for both "free" (Fig. 1) and "bound" (Fig. 2) 211At, as well as the corresponding distribution of the alpha-particles' chord lengths through the nucleus leads to different theoretical cell survival curves for the two irradiation geometries.

![Free Distribution](image)

**Fig. 1.** Distribution [keV⁻¹] of energy deposition per event [keV] to a cell nucleus (r = 5.6 μm) for 211At homogeneously distributed around a cell (r = 7.0 μm)

These theoretical results can be compared with experiments. By irradiating cells with 211At either homogeneously distributed around cells or by using e.g. monoclonal antibodies, distributed on the cell surface, cell survival curves based on either alpha-particle chord length, or energy deposition should reveal which of these two parameters is most relevant for alpha-particle dosimetry.
Fig. 2. Distribution [keV$^{-1}$] of energy deposition per event [keV] to a cell nucleus ($r = 5.6 \, \mu m$) for $^{211}$At bound to cell surface ($r = 7.0 \, \mu m$)

Reference

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FORTHCOMING SCIENTIFIC MEETINGS SCHEDULED BY THE IAEA FOR 1999:

International Seminar on Year 2000 (Y2K): Progress and Co-operation
(Vienna, Austria, 1 - 5 February)

First Review Meeting of Contracting Parties to the Convention on Nuclear Safety
(Vienna, 12-30 April)

International Symposium on Isotope Techniques in Water Resources Development and Management
(Vienna, Austria, 10 - 14 May)

International Symposium on MOX Fuel Cycle Technologies for Medium and Long-Term Deployment: Experience, Advances, Trends
(Vienna, Austria, 17 - 21 May)

International Conference on the Strengthening of Nuclear Safety in Eastern Europe
(Vienna, Austria, 14 - 18 June)

International Symposium on Technologies for the Management of Radioactive Waste from Nuclear Power Plants and Back-end Nuclear Fuel Cycle Activities
(Taejon, Republic of Korea, 30 August - 3 September)

International Symposium on Research Reactor Utilization, Safety and Management
(Lisbon, Portugal, 6 - 10 September)

International Seminar on Mutation Techniques and Molecular Genetics for Tropical and Subtropical Plant Improvement in Asia and the Pacific Region
(Philippines, 11-15 October)

International Seminar on Strengthened International Safeguards: the Record to Date
(Vienna, Austria, 18 - 22 October)

International Conference on Irradiation to Ensure Safety and Quality of Food

International Symposium on Cleanup and Restoration of Sites with Residual Radioactive Materials

Regional Seminar for Asia and the Pacific on Safeguards for the Peaceful Use of Nuclear Energy

International Seminar on Integrated Information Systems

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