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^{188}RHENIUM-HEDP IN THE TREATMENT OF PAIN IN BONE METASTASES

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Abstract

Systemic use of radiopharmaceuticals is a recognised alternative method for the treatment of pain in patients with multiple bone metastases. A new option, ^{188}Re-HEDP is proposed, using generator-obtained ^{188}Rhenium (β energy=2.1 MeV, γ energy=155 keV, half-life= 16.9 hours). After establishing parameters of biodistribution, dosimetry and image acquisition in mice, rats and rabbits, Phase I and II studies were conducted on 12 patients with multiple metastases from carcinomas, with pain surpassing other analgesic options. More than 50% pain relief was found in 91% of the patients, with total relief during a variable period in 41% of them allowing opiate and other analgesic drugs to be decreased or withdrawn, and showing a lower bone marrow contribution to total absorbed dose than that reported for other similar radiopharmaceuticals. Further study of this option is recommended in order to determine higher dose protocols without toxic bone marrow reaction possibilities.

1. INTRODUCTION

Considering death causes in developed countries, cancer is the second in frequency after cardiovascular diseases. Multiple metastases are the common evolution in a high percentage of cancer patients and pain is the main symptom involved. The therapeutical approach to this situation involves chemotherapy, hormonal therapy in cases in which the tumour reacts to hormonal stimulation, radiotherapy and analgesic drugs. In some cases tumours are resistant to hormonal therapy. Local field radiotherapy usually solves the situation in cases of few or single metastatic sites, but as a larger involvement develops, it turns inadequate as a pain relieving tool and the option of hemibody irradiation has significant toxicity. This situation has aroused interest in developing bone-seeking radiopharmaceuticals that can provide less toxic though effective pain relief. After wide initial experience with ^{32}Phosphorus and afterwards with ^{89}Strontium, various phosphonate radiopharmaceuticals were developed, such as ^{186}Rhenium-HEDP and the more used ^{153}Samarium-EDTMP. These compounds have demonstrated favourable biodistribution and dosimetry, and have been approved for clinical use. The objective of the present work is to assess the feasibility of the use of ^{188}Rhenium-HEDP as an option for pain palliation in clinical situations involving multiple metastatic disease. ^{188}Re was obtained from a ^{188}Tungsten/^{188}Rhenium (^{188}W-^{188}Re) radionuclide generator system developed at the Oak Ridge National Laboratory, TN, USA, thus representing an advantage for daily hospital work (1,2). In previously reported work, a lyophilised kit of HEDP for labelling with ^{188}Re was prepared and tested in mice, rats and rabbits showing rapid bone uptake and blood clearance with high renal excretion and good quality images were obtained using the 155 keV gamma photon (3)

2. MATERIALS AND METHODS

2.1- PATIENTS

Twelve patients were selected for treatment after they have provided written informed consent, all suffering from pain caused by multiple metastatic disease. The original cancer was from prostate (n=6), breast (n=5) and uterus (n=1). The Ethical Committee of the University Hospital, School of Medicine, Montevideo, Uruguay approved the protocol used.

Admission criteria were: a) presence of painful bone metastases; b) failure of previous

conventional analgesic therapy; c) bone scan showing multiple bone metastases; d) white blood cells and platelet count higher than 4.000/mm3 and 150.000/mm3 respectively; serum creatinine concentration of 1.5 mg/dl or less.

Exclusion criteria were: a) urinary obstructive pathology; b) renal failure; c) urinary incontinence; d) psychiatric disorders; e) spine compression; f) fracture on pathological bone.

2.2 - PROTOCOL

The total dose was divided in a tracer dose and a complementary therapeutic dose. The tracer dose was administered as an intravenous bolus through a 3-way stopcock and flushed with saline solution. The first 5 patients were followed by serial blood sampling and urine collection during 24 hours. For the rest of the patients urine was collected at time intervals up to 6 hours after dose administration. Bladder catheterization was performed to all the patients in order to facilitate urine collection and minimise possible contamination, as well as to avoid possible urinary retention due to obstructive pathology and to diminish bladder wall irradiation. After 24-48 hours, the complementary therapeutic dose was delivered, following the same procedure. Two patients received a second therapeutic dose, 3-4 months after the first dose. One of the patients was accepted even though his platelet count was less than the admitted limit, because of humanitarian reasons.

Radiopharmaceutical: ^{188}Re-HEDP (radiochemical purity > 98%) has been prepared from lyophilised kits with ^{188}Rhenium from the alumina ^{188}W / ^{188}Re generator provided by Oak Ridge National Laboratory.

Dose: Maximum administered activity limit for accumulated dose was established at 35 mCi (1.3 GBq); 0.45 ±0.09 mCi/kg (16.7±3.3 MBq/kg) considering safety as well as reasonable expectance of therapeutic benefit.

Image acquisition: Whole body scans were performed with a Sophycamera DSX (93 PMT) with a Medium Energy High Resolution collimator, with a 20% window centered at the 155 keV peak.

Sample processing and measurements: One ml of blood was measured for total activity, and centrifuged for plasma separation. Plasma was treated for protein binding by trichloroacetic acid (TCA) precipitation and radioactivity measurements of plasma, TCA supernatant and precipitate were performed. Total recovered volume of urine was measured and aliquots of 20 ml were assayed for radioactivity in a dose calibrator. Multiple regression analysis of blood and plasma profiles was done. Calculation of coefficient and microconstants were obtained by model fitting and elimination half-life (k_e) was calculated from urine profiles by: $\ln(1-E/A_0) = -k_0 t$, where E is urine activity at time t and A_0 is the administered dose. Bone uptake as remnant dose at 24 hours was estimated as $A_0 - E_{max}$ where A_0 is the ^{188}Re-HEDP administered dose and E_{max} is total accumulated urine excretion.

Patient follow-up: After dose administration, patient control was performed by means of weekly interviews during 11 weeks approximately. This control consisted in: a) haematological follow-up by hemogram which included platelet, white and red cell count; b) clinical interview with physical examination of the patient and control of medication status. This evaluation was complemented by daily self-assessment of pain and drug intake, performed by means of protocol forms supplied to the patient or relative in charge, for daily record of pain using a 0-5 subjective pain scale and a drug intake register, in which the amount and kind of pain medication was recorded.

Dosimetry: Residence time in trabecular bone was considered equal to that of cortical bone, and calculated based in experimental data as follows:

Residence time = (0.5 x C/A x 1.443 x $t_{1/2}$ ^{188}Re)h

where :

C - Bone uptake (mCi)

A - Administered dose (mCi)

$t_{1/2}$ ^{188}Re - 16.9 h

Dose absorbed to bone marrow was calculated using MIRDOSE3, introducing residence times.

3) RESULTS

For a total of 14 doses in 12 patients, only 2 doses resulted in no pain relief (14%). Five of the patients experimented periods of total relief of different duration (Table).

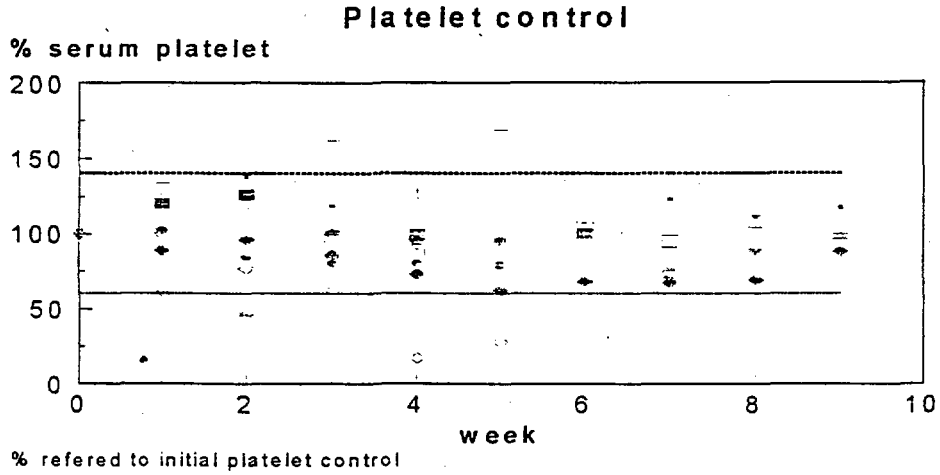
RESULTS: PAIN RELIEF
DOSES : 14

- ONSET
  - » 1 WEEK 3 PTS
  - » 2 WEEKS 6 PTS
  - » 3 WEEKS 2 PTS
  - » 4 WEEKS 1 PT
  - » NO RELIEF 2 PTS
- DURATION
  - » 6 WEEKS 2 PTS
  - » 5 WEEKS 2 PTS
  - » 3-4 WEEKS 5 PTS
  - » 2 WEEKS 2 PTS
  - » 1 WEEK 1 PT

Concerning drug intake, 4 patients were able to discontinue opiate therapy and 3 patients other analgesic drugs. Decrease in drug intake was observed in 7 cases for opiate treatment and in 5 cases of non opiate analgesics.

For the first 5 patients, followed up to 24 hours, bone uptake after therapeutic dose administration showed a mean ± standard deviation of 38 ± 17 %. For the remaining 7 patients, having received 9 administrations, estimated 24 hours uptake was: 41 ± 17 % and 37 ± 16 % for tracer and therapeutic doses respectively. Twenty-four hour bone uptake for all the 12 patients for therapeutic dose administration was estimated as 40 ± 16 %.

Platelets showed mild variations in all but one patient who had a significative decrease in his count. This was the same patient that began the treatment with a lower than recommended platelet count. Nevertheless, no hemorragic symptoms were observed, and platelet count began increasing slowly with no additional treatment. Red cell count showed no variation, and white cells suffered a mild decrease in the same patient of the platelet decrease, and an increase in other patient, from the fifth week onwards.



Platelet Control Graph shows platelet count values of the 12 patients presented as percent of the initial value for each patient.

The 14 doses (tracer and therapeutic) of ^{188}Re-HEDP, administered to the 12 patients had a mean activity of 31 ± 6 mCi. Considering estimated bone uptake of 40 ± 16 % and a residence time of 4.7 ± 1.8 hours, using MIRDOSE3, a bone marrow dose of 2.2± 0.8 rad/mCi and a total bone marrow dose of 65 ± 28 rads were calculated.

4) DISCUSSION

The protocol used to characterise the pharmacokinetic behaviour of ^{188}Re-HEDP was carried on in five patients in a limited study approved by the Ethical Committee. Prosecution of this protocol in a second population discontinued blood sampling for testing radiopharmaceutical clearance and was limited to urine determinations with bladder catheterization up to six hours. Considering that 70% of total eliminated activity was achieved at 6 hours, it was decided that it was not necessary to keep the patient under hospitalisation neither for urine collection nor for radioprotection reasons. After tracer and therapeutic doses, similar blood clearances were observed for the first 5 patients (4). This were also in agreement with the values reported for ^{99m}Tc-HEDP, except for long times where higher values were determined for ^{188}Re-HEDP. A three compartment model was the best fit for the five patients. Urine profiles show that even considering a 60% elimination of injected dose in 24 hours, a rapid excretion occurs in the first 6 hours post administration. No significant differences were found between estimated (n=14) and experimentally determined 24 hour elimination data (n=5). Similar results were also obtained when comparing elimination data after tracer and therapeutic doses. Determination of bone uptake is valuable for dosimetry purposes to critical organ as well as for assessment of a potential correlation between this value and the therapeutic response as pain relieving agent.

Considering blood elements follow up, red cells suffered almost no variation after ^{188}Re-HEDP administration, while platelet and white cells variation referred to initial values was relatively mild. The only exceptions were:

a) One patient whose initial platelet count was lower than recommended, was in a terminal stage and dose was decided on humanity reasons, suffered a platelet and white cell number decrease followed by an increase, and died on the fifth week not from haematological alterations.

b) Another patient who showed an important white cell increase from the 5th week onwards that could be explained by intercurrent infection.

Dosimetry estimations showed that not only a higher bone uptake is indicative of higher absorbed doses to bone marrow, but also that residence time is an important parameter that can be evaluated through urine samples. Comparing estimated bone marrow absorbed dose values in rad/mCi for other therapeutic bone radiopharmaceuticals (^{32}P=14, ^{89}Sr=50, ^{186}Re-HEDP=3, ^{153}Sm-EDTMP=6), ^{188}Re-HEDP absorbed dose has been estimated in 2 rad/mCi.

Comparative series (5,6) using generator or irradiation obtained ^{188}Re, and reporting similar number and pathology patients, tested increasing doses of the radiopharmaceutical with haematological 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.

5) CONCLUSIONS

The use of short-lived, generator-produced ^{188}Rhenium as a bone seeking agent under the form of a phosphonate complex is a promising alternative for pain palliation in patients with multiple bone metastases. As an advantage, the use of long-lived generators makes Re-HEDP a very interesting choice in terms of cost-benefit and availability. For ^{188}Re-HEDP, very good quality radionuclide, low carrier amount and low contamination factor with low radionuclidic impurities ensures a safe performance and good therapeutic results. Further study is still required in order to increase the number of treated patients and to determine the doses and treatment timing that can achieve better results.

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REFERENCES

1) Reactor produced radioisotopes from ORNL for bone pain palliation. F.F. Knapp, S.Mirzadeh, A.L.Beets, M.O'Doherty ,P.J.Blower, S.Verdera, P.J.Gaudiano, J.Kropp, J.Guhlke, H.Palmedo, H.J.Biersack. Appl. Radiat. Isot. Vol 49, N. 4 ,pp. 309-315,1998

2) ^{188}W-^{188}Re Generator for Biomedical Applications. H.Kamioki, S.Mirzadeh, R.M.Lambrecht, F.F.Knapp,Jr. K.Dadachova. Radiochimica Acta 65, 39-46 (1994)

3) Rhenium-188-HEDP-kit Formulation and Quality Control. S.Verdera, J.Gaudiano,A. León, G.Martínez, A.Robles, E.Savio, E. León, D.W.McPherson F.F.Knapp, Jr. Radiochimica Acta 79,113-117(1997).

4) Rhenium-188-HEDP: Pharmacokinetics Characterization in Osseous Metastasic and Clinical Evaluation. E. Savio, J. Gaudiano, A. Robles, G. Martínez, A. León, S. Verdera, S. Muñiz, J.C. Hermida and F.F. Knapp, Jr. (submitted)

5) Rhenium-188(Sn) HEDP for Treatment of Osseous Metastases. H. R. Maxon,III, L.E. Schroder, Lee C. Washburn, S.R.Thomas, R.C. Samaratunga, D. Binlakiewiez, J. S. Moulton, D. Cummings, G. J. Ehrhadt and V. Morris. J. Nucl. Med 1998, 39:659-663.

6) Rhenium-188 HEDP Bei Multiplen Knochen-Metastasen: Eine Dosisfindungs-Studie. H. Palmedo, S. Guhlke, H. Bender, J. Sartor, F.F. Knapp, M. Bangard, R. Otte, H.J. Biersack.Deutsche Gesellschaft fur Nudklarmedizin e. V. 36. Internationale Jahrestagun, 01.04. April 1998, Leipzig.