THE PRODUCTION OF CYCLOTRON RADIOISOTOPES AND RADIOPHARMACEUTICALS AT THE NATIONAL ACCELERATOR CENTRE IN SOUTH AFRICA

T.N. VAN DER WALT
National Accelerator Centre,
Faure, South Africa

Abstract

Accelerator radioisotopes have been manufactured in South Africa since 1965 with the 30 MeV cyclotron at the Council for Scientific and Industrial Research (CSIR) in Pretoria. After its closure in 1988, the radioisotope production programme was continued at the National Accelerator Centre (NAC) with the 200 MeV separated-sector cyclotron (SCC) utilizing the 66 MeV proton beam, which is shared with the neutron therapy programme during part of the week. A variety of radiopharmaceuticals, such as ^{18}F-FDG, ^{67}Ga-citrate, a ^{67}Ga-labelled resin, ^{111}In-chloride, ^{111}In-oxine, an ^{111}In-labelled resin, ^{123}I-sodium iodide and ^{123}I-labelled compounds, ^{201}Tl-chloride, as well as the ^{81}Rb/^{81m}Kr gas generator, are prepared for use in the nuclear medicine departments of 12 State hospitals and about 28 private nuclear medicine clinics in South Africa. A few longer-lived radioisotopes, such as ^{22}Na, ^{55}Fe and ^{139}Ce, are also produced for research or industrial use. A research and development programme is running to develop new production procedures to produce radioisotopes and radiopharmaceuticals, or to improve existing production procedures. As part of a programme to utilize the beam time optimally, the production of some other radioisotopes is investigated.

1. INTRODUCTION

The National Accelerator Centre is a multidisciplinary research centre and is operated by the Foundation for Research Development (FRD) as a national facility. It provides accelerator and ancillary facilities for use on a national basis for :

(a) Research and training in the physical, chemical and biomedical sciences.

(b) Research in and the treatment of cancer with neutrons and charged particles.

(c) The development of new or improved production procedures for radioisotopes for use in research, industry and in radiopharmaceuticals.

(d) The development of new radiopharmaceuticals for use in nuclear medicine for diagnostic studies.

The NAC is the only particle therapy facility in the Southern Hemisphere and the only one in the world where both high energy neutrons and high energy protons are used for patient treatment. One of the treatment vaults contains the isocentric neutron therapy unit (66 MeV p/Be), while the 200 MeV horizontal proton beam therapy facility occupies a second vault. A second vertical proton therapy line is foreseen for a third vault.

2. RADIOISOTOPE PRODUCTION PROGRAMME

The 66 MeV beam is utilized for radioisotope production. Proton therapy takes place on Mondays, Tuesdays, Wednesdays and Thursdays, and neutron therapy on Tuesdays, Wednesdays and Fridays. The 200 MeV proton beam is used for nuclear physics research over the weekend. However, because of the tight time schedule, radioisotope production can only be done during night time (from about 20h00 until 06h00 the next morning) on Mondays, Wednesdays and Thursdays. The production of ^{67}Ga usually starts Monday evening and the bombardment of the zinc target continues (during night time), with a few interruptions of the bombardment, until Thursday morning. During these interruptions other radioisotopes, such as ^{18}F, ^{22}Na, ^{81}Rb, ^{111}In, ^{123}I, ^{139}Ce and ^{201}Tl, are produced. The chemical separation procedure to recover the appropriate radioisotope from the target material usually starts immediately after the end of the bombardment.

Table I shows the production details for ^{18}F, ^{22}Na, ^{55}Fe, ^{67}Ga, ^{81}Rb, ^{111}In, ^{123}I, ^{139}Ce and ^{201}Tl. The bombardment takes place in a bombardment station and the target usually consists of a metal or salt disc which is encapsulated in an aluminium can. At the end of the bombardment the target is transported to a hot-cell and the aluminium can cut open. The target is removed and transported to the processing hot-cell to recover and purify the appropriate radioisotope. The highly-pure radioisotope is then converted to the required radiopharmaceutical form, which is dispensed and dispatched to the nuclear medicine centres by road or by air.

Table I. Radioisotope production details.

Radionuclide	Production Reaction(s)	Target Material	Bombardment Energy (MeV)	Beam Current (μA)
^{18}F	$Ne(p,X)^{18}F$	Ne	63.0 – 58.3	20
^{22}Na	$Mg(p,X)^{22}Na$	Mg	61.5 – 40.0	80
^{55}Fe	$Mn(p,n)^{55}Fe$	Mn	35.2 – 11.0	80
^{67}Ga	$Zn(p,xn)^{67}Ga$	Zn	36.7 – 21.9	80
	$Ge(p,X)^{67}Ga$	Ge	61.5 – 38.5	80
$^{81}Rb/^{81m}Kr$	$Kr(p,xn)^{81}Rb$	Kr	52.5 – 45.0	30
	$Rb(p,X)^{81}Rb$	RbCl	62.9 – 57.7	65
^{111}In	$In(p,xn)^{111}Sn \rightarrow {}^{111}In$	In/In_2O_3(55/45)	62.6 – 54.2; 53.0 – 43.4	80
^{123}I	$I(p,5n)^{123}Xe \rightarrow {}^{123}I$	NaI	62.9 – 47.9	65
^{139}Ce	$Pr(p,X)^{139}Ce$	Pr	61.5 – 20.0	80
^{201}Tl	$Tl(p,xn)^{201}Pb \rightarrow {}^{201}Tl$	Tl	28.6 – 21.0	30

Table II. Radioisotopes for medical and non-medical use produced and supplied to users during the period 1 April 1996 to 31 March 1997 (with corresponding values for the previous 12 months in brackets).

	Radiopharmaceutical	**Consignments**	**Activity (MBq)**
MEDICAL RADIOISOTOPES	^{18}F-solution	1 *(5)*	876 *(10849)*
	^{18}F-FDG	3 *(5)*	936 *(2233)*
	^{67}Ga-citrate	493 *(503)*	257520 *(283312)*
	^{81}Rb/^{81m}Kr-generators	187 *(250)*	103785 *(138138)*
	^{123}I-NaI-solutions	52 *(50)*	11789 *(9364)*
	^{123}I-NaI-capsules	47 *(38)*	15179 *(12286)*
	^{123}I-mIBG	203 *(183)*	65858 *(58336)*
	^{123}I-IPPA	3 *(13)*	765 *(2273)*
	^{123}I-BMIPP	15 *(16)*	3419 *(3110)*
	^{123}I-VIP	9 *(8)*	1010 *(1768)*
	^{123}I-epidepride	4 *(0)*	1057 *(0)*
	^{123}I-epidepride deriv.	2 *(0)*	549 *(0)*
	^{201}Tl-chloride	32 *(24)*	5220 *(3434)*
NON-MEDICAL RADIOISOTOPES	**Radioisotope**	**Consignments**	**Activity (MBq)**
	^{22}Na	7 *(8)*	10854.6 *(13673)*
	^{139}Ce	1 *(0)*	2800 *(0)*
	^{111}In	11 *(10)*	1710 *(1716)*

The ^{18}F, ^{67}Ga, ^{81}Rb, ^{111}In, ^{123}I and ^{201}Tl are used to prepare the following radiopharmaceuticals for diagnostic studies at nuclear medicine centres :

^{18}F-FDG, ^{67}Ga-citrate, a ^{67}Ga-labelled resin, the $^{81}Rb/^{81m}Kr$ gas generator, ^{111}In-chloride, ^{111}In-oxine, an ^{111}In-labelled resin, ^{123}I-sodium iodide and ^{123}I-labelled organic compounds and ^{201}Tl-chloride (Table II).

Table II shows the medical radioisotopes delivered to nuclear medicine centres in South Africa and the non-medical radioisotopes produced during the 1996/1997 financial year.

3. RESEARCH AND DEVELOPMENT PROGRAMME

Chemical procedures have been developed for the recovery and purification of various radioisotopes from the bombarded targets, the preparation of labelled compounds, as well as quality control methods [1-6]. Nuclear data measurements have also been done at the NAC [7-10].

Research is continuously carried out to develop new methods, or to improve existing methods, for the recovery and purification of radioisotopes from the target materials. As part of a programme to utilize the beam time optimally, the production of some other radioisotopes is investigated. The labelling of organic compounds with ^{123}I to prepare new radiopharmaceuticals is also being investigated. New studies, which will begin soon, are those for the production of ^{75}Se, $^{82,83}Sr$, ^{103}Pd, ^{124}I and ^{124}I-labelled compounds. In a joint research and development project with the Forschungszentrum Jülich in Germany the excitation functions of $^{125}Te(p,2n)^{124}I$, $^{126}Te(p,3n)^{124}I$ and $^{85}Rb(p,3n)^{83}Sr$ reactions from thresholds up to 70 MeV will be measured. Therefrom, the optimum conditions for the production of ^{124}I and ^{83}Sr will be determined.

4. THE ACQUISITION OF A DEDICATED 70 MeV CYCLOTRON FOR THE PRODUCTION OF RADIOISOTOPES AND NEUTRON THERAPY

The two solid-pole injector cyclotrons and the SCC accelerate beams of charged particles to various energies for (a) nuclear physics research, (b) radioisotope production and (c) proton and neutron therapy. The cyclotrons have been operated since July 1996 according to an extremely tight schedule based on nine energy changes per week, required by the internationally-accepted daily treatment schedule for patients with protons (200 MeV) and neutrons (using 66 MeV protons). As the main components of the SSC and the injector cyclotrons have now been in operation for 14 years, the rate of unexpected failures have increased significantly. This is partly due to ageing, wear-and-tear, corrosion, radiation damage, etc., but mainly because of the repeated electrical and mechanical cycling of the magnets, radiofrequency systems and other components of the cyclotrons and beam lines during energy changes. As a consequence of the much tighter time schedule and increased rate of failure, unplanned emergency repairs often have to be carried out during the already limited beam time available for the production of radioisotopes and neutron therapy. Since the various radioisotopes are only produced once per week no additional production run can be carried out. This causes a lot of discomfort to the nuclear medicine community and the patients, and causes a loss of income to the NAC. The continuous supply of cyclotron-produced radioisotopes is vital to the Health Sector in South Africa since short-lived radioisotopes cannot be imported economically. The rescheduling of diagnostic studies or neutron therapeutic treatments to other days is detrimental to patients, and wasting valuable time of radiographers and radiotherapists who travel to the NAC to supervise treatments. Therefore, the NAC plans to purchase a 70 MeV cyclotron in the future if it can obtain money from the government or elsewhere.

5. CONCLUSION

The NAC produces highly-pure radioisotopes which are used for the preparation of important radiopharmaceuticals for diagnostic nuclear medicine. It also produces longer-lived radioisotopes, mainly for the export market. The NAC is a centre of excellence for research in the physical, chemical and biomedical sciences and a lot of students (diploma, degree and post-graduate) benefit from the training and research done at the NAC.

REFERENCES

[1] VAN DER WALT, T.N., STRELOW, F.W.E., HAASBROEK, F.J., "Separation of iron-55 from manganese cyclotron target material on a 2% cross-linked anion exchanger in hydrochloric acid", Int. J. Appl. Radiat. Isot. **36** (2) (1985) 159-161.

[2] VAN DER WALT, T.N., COETZEE, P.P., "Separation of ^{201}Tl by anion exchange chromatography on AG 1-X4 after proton bombardment of a lead cyclotron target", S. Afr. J. Chem. **42** (2) (1989) 64-67.

[3] VAN DER WALT, T.N., HAASBROEK, F.J., "The separation of ^{22}Na from magnesium cyclotron targets by ion exchange chromatography in alkaline medium", Synthesis and Applications of Isotopically Labelled Compounds (Proc. Fifth Int. Symp., Strasbourg, France, 20-24 June 1994) ALLEN, J., VOGES, R., Ed., John Wiley & Sons Ltd., New York (1995) 211-214.

[4] BRITS, R.J.N., STRELOW, F.W.E., "^{67}Ga/Zn Separation with an Organic Adsorbent", Appl. Radiat. Isot. **41**, (1990) 575-578.

[5] ROSSOUW, D.duT., "Routine Production and Quality Control of ^{123}I-Labelled mIBG at NAC", Appl. Radiat. Isot. **43** (1992) 1301-1302.

[6] ROSSOUW, D.duT., LANGENHOVEN, J.H., "Improved Radiosynthesis of 2-[^{123}I]Iodomelatonin", Appl. Radiat. Isot. **45** (1994) 902-904.

[7] NORTIER, F.M., MILLS, S.J., STEYN, G.F., "Excitation functions and yields of relevance to the production of ^{67}Ga by proton bombardment of ^{nat}Zn and ^{nat}Ge up to 100 MeV", Appl. Radiat. Isot. **42** (1991) 353-359.

[8] STEYN, G.F., MILLS, S.J., NORTIER, F.M., HAASBROEK, F.J., "Integral excitation functions for ^{nat}Kr + p up to 116 MeV and optimization of the production of ^{81}Rb for ^{81m}Kr generators", Appl. Radiat. Isot. **42** (1991) 361-370.

[9] NORTIER, F.M., MILLS, S.J., STEYN, G.F., "Excitation functions for the production of ^{109}Cd, ^{109}In and ^{109}Sn in proton bombardment of indium up to 200 MeV", Appl. Radiat. Isot. **42** (1991) 1105-1107.

[10] STEYN, G.F., MILLS, S.J., NORTIER, F.M., "The production of ^{55}Fe with medium-energy protons", Appl. Radiat. Isot. **43** (1992) 1323-1327.