Journal of Radioanalytical Chemistry, Vol. 27 (1975) 129–136

Analytical Control of Radiopharmaceuticals Section

PRESENT AND FUTURE OF RADIOPHARMACEUTICALS RESULTING FROM GENERATORS

A. E. A. MITTA

Radioisotopes Department Comision Nacional de Energia Atomica, Buenos Aires (Argentina)

(Received March 17, 1975)

The production method, the advantages and disadvantages of some radiopharmaceutical produced in different generators are shown. Considerations are given with respect to the frequently used generators.

Introduction

The first radionuclide applications in nuclear medical diagnosis started in 1938 with HERTZ and HAMILTON. During several years radiopharmaceutical produced and controlled by specialized laboratories were used. One of the major advances in nuclear medicine in the last decade has been the introduction of the routine use of radiopharmaceuticals obtained from generators.

This means preparations "in situ" which requires to provide new installations and the application of a chemist at the hospital to ensure the quality of the radiopharmaceutical by means of quick control methods before its application to the patient.[1]

Generators and radiopharmaceuticals

The generator is based on the parent – daughter equilibrium, the first being of relatively long half-life and the second of relatively short one which is useful in its application in diagnosis or "in vivo" therapy.

The parent's long half-life allows the generator to be sent to the user and the radionuclide daughter can be separated from the parent by a simple chemical method.

Besides the generator must have the necessary radiological protection so that the people handling it could operate safely and, when it is destined to medical use, precautions should be taken so as to obtain a sterile solution out of it.[2]

The first idea of a generator for medical use was that of GIOACHINO FAILLA, who in 1920 suggested the following generator:

$$^{226}Ra \xrightarrow{1620\ y} {}^{222}Rn \xrightarrow{3.8\ d} {}^{218}Po, \qquad 352\ keV$$

for probable use in therapy.[3]

Some years later, by the end of 1950, STANG et al.[4] from the Brookhaven National Laboratory, developed an artificial generator.

$$^{132}Te \xrightarrow{3.2\ d} {}^{132}I \xrightarrow{2.3\ h} {}^{132}Xe$$

Implying a halogen, this generator was first thought to have a great future, but it was overestimated.

The most common generators which can be purchased commercially are indicated in Table 1, the first two represent 99% of the production.

From the above indications the $^{99}Mo/^{99m}Tc$ generator, described by RICHARD in 1957, but whose design was later modified, is the most employed one at present time.

There are several ways to get ^{99m}Tc:

(1) From molybdenum trioxide by sublimation;

(2) From MoO_3 by solvent extraction (methylethylketone);

(3) If the generator is an Al_2O_3 column with adsorbed ^{99}Mo, this can be extracted from it by a suitable eluent (phisiological solution).

The third method is the most widely used, although in some countries e.q. Australia, the first and second methods are employed.[5]

At the beginning, the production method for ^{99}Mo was neutron bombardment of natural Mo or ^{98}Mo enriched molybdenum. At the present time the ^{99}Mo obtained from fission products can also be used, this one is of very high specific activity; it is suitable for use alone or in preparations of radiopharmaceuticals for dynamic studies.

The cost of the generator using ^{99}Mo obtained from fission products is high and besides the activity concentration of the ^{99m}Tc after the first days of use decreases. For dynamic studies this makes it necessary to employ it in patients as soon as possible.

Table 1
The most common generators for producing radiopharmaceuticals

Parent		Daughter			Decomposition procedure	Principal energy, keV	Year
^{99}Mo	$\xrightarrow[67\ h]{\beta,\gamma}$	^{99m}Tc	$\xrightarrow[6\ h]{\gamma}$		^{99}Tc	140	1962
^{113}Sn	$\xrightarrow[119\ d]{CE}$	^{113m}In	$\xrightarrow[1.7\ h]{\gamma}$		^{113}In	392	1966
^{87}Y	$\xrightarrow[80\ h]{CE\ \gamma}$	^{87m}Sr	$\xrightarrow[2.8\ h]{\gamma}$		^{87}Sr	388	1967
^{68}Ge	$\xrightarrow[280\ d]{CE}$	^{68}Ga	$\xrightarrow[68\ m]{CE,\beta^+}$		^{68}Zn	511	1960
^{132}Te	$\xrightarrow[3.2\ d]{\beta,\gamma}$	^{132}I	$\xrightarrow[2.3\ h]{\beta,\gamma}$		^{132}Xe	670	1950
^{137}Cs	$\xrightarrow[30\ y]{\beta,\gamma}$	^{137m}Ba	$\xrightarrow[2.6\ m]{\gamma}$		^{137}Ba	622	1969
^{90}Sr	$\xrightarrow[2.8\ y]{\beta}$	^{90}Y	$\xrightarrow[68\ h]{\beta}$		^{90}Zr	2250	1957

In 1973 BENES and De SCHRIJVER[6] presented a method to concentrate the eluate in a column and to use it in the preparation of radiopharmaceuticals. In this method the ^{99m}Tc of the eluate ($\pm 10^{-6}$ mg/ml) is precipitated with ferrous hydroxide according to the reaction:

$$Fe(OH)_2 \xrightarrow{^{99m}TcO_4^-} Fe(OH)_3 \cdot Tc(IV)$$

and then redissolved in HCl to prepare the radiopharmaceutical using the reaction:

$$SnCl_2 \xrightarrow{^{99m}TcO_4^-} Sn(OH)_4 \cdot Tc(IV)$$

We have carried out the same procedure with very good results.[7] This allowed us to prepare almost all Tc radiopharmaceuticals (the former authors prepared just a few of them). The advantages of the use of ^{99m}Tc are as follows:

(1) Its low energy radiation (140 keV) limits radiation danger for the patient in case of injection by mistake;

(2) Due to its 6 hrs half-life some quality controls can be performed before sending it to the user;

(3) For the same reason it is possible to centralize the preparation of the radiopharmaceuticals for its subsequent distribution;

(4) The column can be eluted once a day, or twice if necessary;

(5) Due to its low disintegration energy (140 keV) the personnel working with this material needs simple blindage;

(6) Its effective half-life results in low radiation doses to the patient. Its radiation characteristics provides a high efficiency detection;

(7) The possibility of preparing a great quantity of radiopharmaceuticals (more than with any other generator: see Table 2) though it is a foreign element to the organism.

The disadvantages of the application of ^{99m}Tc are:

(1) It requires frequent deliveries. This increases the cost in the case of few applications;

(2) Too long a half-life for some studies;

(3) Some deep lesions cannot be detected because of its low penetration;

(4) The valence can change by contamination with reducing materials this produces radioactive impurities.

Its main rival is the ^{113}Sn/^{113}In generator with the following advantages:

(1) Relative minor cost because it lasts approximately 6 months;

(2) Compatible with equipments using ^{131}I because it has similar energy;

(3) It fixes quickly to plasma transferrin after injection;

(4) Using an acid eluent the bacterial contamination risk diminishes.

Its disadvantages are:

(1) Considerable radiation danger for a patient injected by mistake due to its radiation energy of 392 keV;

(2) Low efficiency with gamma camera;

(3) Thick blindage is needed;

(4) Uneconomic in case of contamination by use of a fair eluent;

(5) The radiopharmaceuticals which can be prepared with ^{113m}In are seen in Table 3.

As in the case of ^{99m}Tc the generator activity decays after several months and a large volume of eluate is needed to obtain a few mCi. W. CALISTO and A. M.

Table 2
^{99m}Tc Radiopharmaceuticals

Radiopharmaceutical	Organ
(1) Sodium pertechnetate $^{99m}TcO_4Na$	Brain
D.T.P.A. $CaNa_3$ (Sn) ^{99m}Tc	
(2) D.T.P.A. $CaNa_3$	Kidneys
Ca. Gluconate	
Na. Lactobinate	
Na. Glucoheptanate	
Dextrose	
Manitol	
Lactose	
Penicillamine	
2.3-Dimercaptosuccinic acid	
(3) Technetium sulfur	Liver
Tin hydroxide	
Sodium phytate	
(4) Inorganic macroaggregates	Lungs
Albumine macroaggregates	
Microspheres (30 μ)	
(5) Polyphosphates	Bones
Diphosphonate	
Pyrophosphate	
Monofluorophosphate	
(6) Albumine	Dynamic studies
Millimicrospheres (0.5 mμ)	
(7) Bleomycin	Tumor
Citrate	
Tetracycline	
(8) Red Blood corpuscules	Spleen
(9) Biliar acids	Biliar functions

Table 3
Radiopharmaceuticals produced with ^{113m}In

Radiopharmaceutical	Organ
$^{113m}In\ Cl_3$	Placenta localization
^{113m}In macroaggregates	Lung
^{113m}In microaggregates	Liver
D.T.P.A. ^{113m}In	Brain and kidney

ROBLES of Uruguay[8] have developed a method to concentrate the activity of a $^{113}Sn/^{113m}In$ column to 0.5 ml after decay. It consists in precipitating ^{113m}In with 0.5N NaOH, filtering through Millipore syringe, and redissolving it in a small volume of HCl 0.005N.

The following considerations can be made with respect to the other generators giving in Table 1:

$^{87}Y/^{87m}Sr$. ^{87m}Sr has some advantages as compared to other strontium isotopes, viz. its short half-life and monoenergetic γ-radiation of 392 keV. Its disadvantages are the parent's short half-life and the necessity of preparing it in a cyclotron:

$$^{85}Rb(\alpha, 2n)^{87}Y, \qquad ^{87}Sr(p, n)^{87}Y$$

$^{68}Ge/^{68}Ga$. It is a β^+ emitter useful for scintigraphy of bones, brain, liver, spleen, bone marrow.

The main advantage is its long parent's half-life.

Its disadvantage is that it must be prepared in a cyclotron in a process of $^{69}Ga(p, 2n)^{68}Ge$.

$^{132}Tc/^{132}I$. It is used in children's thyroid studies. It has bad energetic characteristics and a short parent's half-life.

$^{137}Co/^{137m}Ba$. γ-emitter of 662 keV used in dynamic studies. The long parent's half-life facilitates the possibility of contamination with the daughter.

$^{90}Sr/^{90}Y$. High energy β-emitter, used in therapy for pleural and peritoneal treatment.

In Table 4 there are other generators, which had no appreciable development.

This list is incomplete because the number of possible generators is over 100 although not all of them are useful. It is rather difficult to foretell which of them are promising. In Table 5 there is a $^{82}Sr/^{82}Rb$ generator used for myocard studies[12,13] and a "theoretical cow" and ^{77m}Se and ^{195m}Au generators for the same applications.

Table 4
Generators of smaller importance

Parent		Daughter		Decomposition procedure	Principal energy, keV
^{81}Rb	$\xrightarrow[4.7\ h]{\beta^+, CE}$	^{81m}Kr	$\xrightarrow[13\ s]{Tl}$	^{81}Kr	190
^{128}Ba	$\xrightarrow[58.3\ h]{CE, \gamma}$	^{128}Cs	$\xrightarrow[3.8\ m]{CE}$	^{128}Xe	370
^{188}W	$\xrightarrow[69.4\ d]{\beta, \gamma}$	^{188}Re	$\xrightarrow[16.8\ h]{\beta, \gamma}$	^{188}Os	160 360
^{112}Pd	$\xrightarrow[21\ h]{\beta}$	^{112}Ag	$\xrightarrow[3.2\ h]{\beta}$	^{112}Cd	3900
^{28}Mg	$\xrightarrow[21.4\ h]{\beta, \gamma}$	^{28}Al	$\xrightarrow[2.3\ m]{\beta, \gamma}$	^{28}Si	1780
^{103}Pd	$\xrightarrow[17\ d]{\gamma}$	^{103m}Rh	$\xrightarrow[57\ m]{Tl\ \gamma}$	^{103}Rh	40

Table 5
Some other generators

Parent		Daughter		Decomposition process	Principal energy, keV
^{82}Sr	$\xrightarrow[25\ d]{CE}$	^{82}Rb	$\xrightarrow[1.2\ m]{\beta^+\ CE}$	^{82}Kr	511 777
^{77}Br	$\xrightarrow[56\ h]{\beta^+\ CE}$	^{77m}Se	$\xrightarrow[17.5\ s]{Tl\ \gamma}$	^{77}Se	162
^{195m}Hg	$\xrightarrow[40\ h]{CE}$	^{195m}Au	$\xrightarrow[30.5\ s]{Tl\ \gamma}$	$^{195}Au \xrightarrow[183\ d]{CE} {}^{195}Pt$	262
^{81}Br	$\longrightarrow$	^{84m}Rb	$\xrightarrow[20\ m]{CE\ \beta^+}$	^{84}Rb	250

For radiopharmaceuticals resulting from "promising" generators we think that emphasis should be put on compounds for "in vivo" metabolism studies with ^{99m}Tc and also with ^{113m}In for kidney, bones, etc. studies.

Conclusions

It is a general opinion that the ^{99}Mo/^{99m}Tc generator and the radiopharmaceuticals obtained from it will be those of major use for a long time.

The ideal would be generators producing a radionuclide with similar characteristics to those of ^{99m}Tc but with shorter half-life for dynamic studies, and another radionuclide with longer half-life for scintigraphic studies.

Nevertheless, the possibility of a future generator producing a radionuclide as versatile as ^{99m}Tc cannot be excluded.

Anyhow the choice of a radionuclide in a medical service depends greatly of means and possibilities of the users.

References

1. J. J. TOUYA, Proc. IAEA Conf. Medical Radioisotope Scintigraphy, Vienna, 2 (1973) 3.
2. V. I. SPITAYN, N. B. MIKEEV, At. Energ. Rev., 9 (1971) 787.
3. W. R. KORMEKER, Radioactive Pharmaceuticals U.S.A.C. Div. Techn. Inf. Oak Ridge, 1966. p. 186.
4. W. E. WINSCHE, L. G. STANG, W. TUCKER, Nucleonics, 8 (1951) 4.
5. R. E. BOYD, Proc. IAEA, WHO Conf. Radiopharmaceuticals and Labelled Compounds, Vol. 1, Vienna, 1973, p. 3.
6. I. BENES, M. DE SCHRIJVER, XVe Colloque de Medecine Nucleaire de Langue Francaise, 1973.
7. S. G. DE CASTIGLIA, A. H. F. DE SUAREZ, A. E. A. MITTA, V. Congreso de ALASBIMN, La Paz-Bolivia, 3–8 noviembre de 1974.
8. W. CALISTO, A. M. ROBLES, Revista de ALASBIMN, 6 (1974) 45.
9. A. E. A. MITTA, J. ALVAREZ, C. P. RABAN, Proc. IAEA Conf. Radiopharmaceuticals from Generators Produced Radionuclides, Vienna, 1971, p. 67.
10. S. G. DE CASTIGLIA et al., Informe N° 327 CNEA, 1973.
11. M. BRUCER, Isotopes Rad. Tech., 3 (1965) 1.
12. R. HENRY, J. Nucl. Biol. Med., 15 (1971) 105.
13. E. LEBOWITZ, P. RICHARDS, Seminars in Nuclear Medicine, 4 (1974) 257.