SYSTEM FOR SUSTAINED INTRAVENOUS INFUSION OF A STERILE SOLUTION OF ^{137m}Ba-ETHYLENEDIAMINETETRAACETIC ACID (EDTA)

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The quality of a scanning image is determined in part by the number of photons available to the radiation detector. Before the use of generator-produced ^{99m}Tc and ^{113m}In (*1,2*), any increase in photon yield by longer-lived radionuclides substantially increased patient radiation exposure. Generator-produced radionuclides therefore became increasingly more important in nuclear medicine both for scanning and dynamic studies.

The generator-produced ultrashort-lived radionuclides listed in Table 1 were chosen because their mode of decay seemed to have certain advantages in studies of the circulatory system. In such systems, the radiopharmaceutical is infused, and after equilibrium is reached, pharmacodynamic measurements are made. When the study is completed, the infusion is discontinued, and the existing circulating radioactivity rapidly decays. Studies can be repeated at frequent intervals if desired.

The generator system we have studied is the ^{137}Cs-^{137m}Ba system. The ^{137}Cs parent decays with a half-life of 30 years while the ^{137m}Ba daughter decays with a half-life of 2.5 min. This generator system has been used previously in biomedical research (*3–5*), but never as a sustained intravenous infusion.

TABLE 1. GENERATOR-PRODUCED ULTRA-SHORT-LIVED RADIOISOTOPES WITH POSSIBLE BIOLOGICAL APPLICATION

Radionuclide	$T_{1/2}$	Primary photon E (MeV)	Parent	$T_{1/2}$
^{167m}Er	2.5 s	0.208	^{167}Tm	9.6 d
^{191m}Ir	4.9 s	0.192	^{191}Os	16 d
^{183m}W	5.3 s	0.16, 0.21	^{183}Re	70 d
^{81m}Kr	13.0 s	0.19	^{81}Rb	4.7 h
^{77m}Se	17.5 s	0.16	^{77}Br	57 h
^{109m}Ag	39.2 s	0.88	^{109}Cd	1.3 y
^{83}Rb	80.0 s	0.76, 1.4	^{83}Sr	25.5 d
^{137m}Ba	2.6 m	0.662	^{137}Cs	30 y

MATERIALS AND METHODS

Solutions used in this study were:

Solution A: The generator eluting solution and eluate consisted of 0.1 *N* HCl, 0.1 *N* NH_4Cl. Carrier-free $^{137m}BaCl_2$ and ^{137}CsCl pass into the reservoir with the eluate.

Solution B: Sodium (EDTA) 0.005 *N* ethylenediaminetetraacetic acid mixed with a 5 *N* solution of NaOH.

Solution C: A modified phosphate buffer system (*7*) adjusted to isotonicity with physiological saline at a pH of 7.38.

The generator. A 5-mCi ^{137}Cs-^{137m}Ba generator was prepared by a modification of the procedure of van Smit (*6*) and Blau (*3*). One gram of ammonium-phospho-molybdate resin (Bio-Rad AMP-1) was suspended in 25 ml of 0.1 *N* HCl and 0.1 *N* NH_4Cl (Solution A) before preparation of the generator.

One gram of acid-washed asbestos (Powminco) was suspended in 100 ml of Solution A and mixed in a Waring blender for 25 sec. The fine and coarse fibers were removed by washing and decanting four times with 100 ml of Solution A.

The resin and acid-washed asbestos were mixed, and the AMP-1 that did not adhere to the asbestos was removed. A 30-ml glass syringe (Luer-Loc tip) was packed to the 1-ml mark with acid-washed asbestos and glass wool. The resin-asbestos mixture was then added to the 6-ml mark followed by a plug of glass wool and a Teflon retainer ring. The resin bed was then packed to the 5-ml mark.

Five millicuries of carrier-free ^{137}Cs was poured over the prepared column, allowed to flow by grav-

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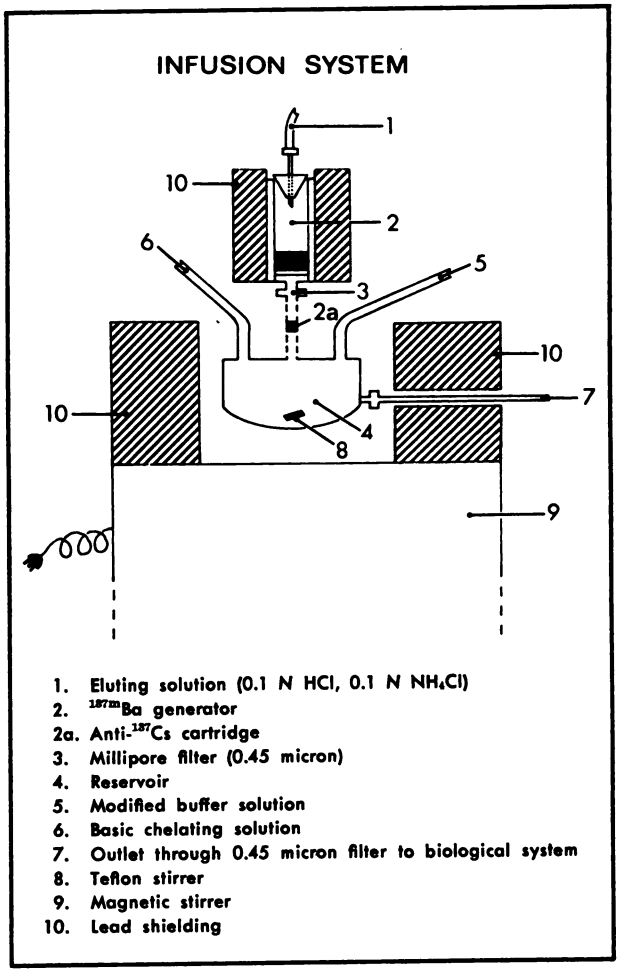

1. Eluting solution (0.1 N HCl, 0.1 N NH_4Cl)
2. ^{137m}Ba generator
2a. Anti-^{137}Cs cartridge
3. Millipore filter (0.45 micron)
4. Reservoir
5. Modified buffer solution
6. Basic chelating solution
7. Outlet through 0.45 micron filter to biological system
8. Teflon stirrer
9. Magnetic stirrer
10. Lead shielding

FIG. 1. ^{137m}Ba generator and infusion system.

ity and collected for evaluation of loading efficiency. The column was then washed with 30 ml of Solution A to remove any residual ^{137}Cs that was not retained during the loading procedure.

A rubber plug with an inserted needle (19G × 1½ in.) was fitted into the top of the generator, and a Teflon tube (i.d. = 3 mm) was attached to one end of the needle. To the other end of the tube a 50-ml glass syringe was attached. The glass syringe was filled with Solution A and placed into the proper fittings of constant infusion pump (Harvard Infusion/Withdrawal Pump, Model 600-900).

The infusion pump supplied Solution A at a rate of 1.91 ml/min. Twenty 2-ml samples were collected and analyzed for pH and isotonicity.

The reservoir system. A diagram of the glass reservoir system, which serves as a reaction vessel, is given in Fig. 1. The solutions were added continuously and were mixed in the reservoir with a Teflon magnetic stirrer and pumped through a Millipore 0.45-micron filter.

The product. The reservoir was prefilled with 100 ml of the modified phosphate buffer system, and Solutions A, B and C were simultaneously added at 1.91 ml/min each. Thirty 10-ml samples of the resulting infusate were collected and analyzed for ^{137m}Ba yield, ^{137}Cs contamination, pH and isotonicity.

The anti-^{137}Cs cartridge. To lower the ^{137}Cs contamination as much as possible, a micro-ammonium-phospo-molybdate cartridge was developed. A 14 × 1-cm cartridge was prepared according to the procedure for the generator and placed between the primary column and the reservoir.

The infusate was analyzed with and without this micro-column for ^{137m}Ba yield, ^{137}Cs contamination, pH and isotonicity.

Constant infusion of ^{137m}Ba-chelate into a dog. The reservoir was prefilled with 100 ml of the modified phosphate buffer solution. A Millipore disposable filter unit (0.45-micron filter) was attached to outlet d (Fig. 1). The reservoir was infused into a peripheral vein of a dog's left foreleg at a rate of 5.7 ml/min. Once the radiopharmaceutical reached equilibrium in the dog, as determined by a stable counting rate, a cardiac blood-pool scan was performed using a rectilinear photoscanner with a 5 × 2-in NaI(Tl) crystal. A 43-hole positron collimator with an upper septal thickness of 0.418 cm and a lower septal thickness of 0.178 cm was used because of the high gamma energy (0.662 MeV) of ^{137m}Ba. A cardiac blood-pool scan of a dog was obtained (Fig. 2) during the constant infusion of ^{137m}Ba-EDTA.

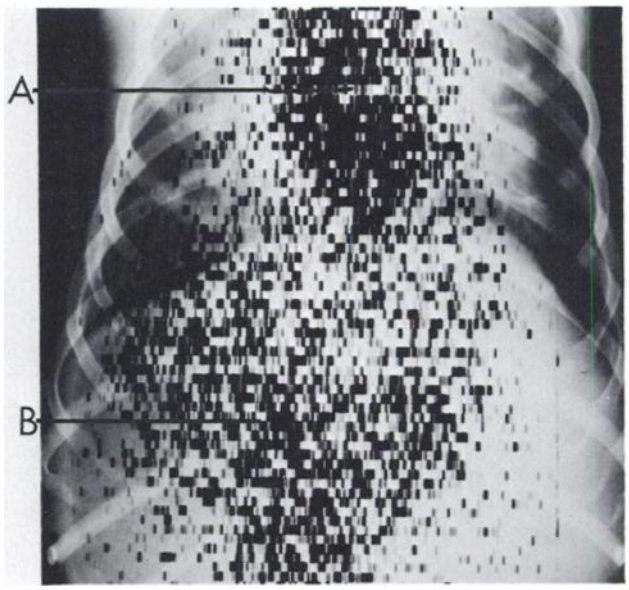

FIG. 2. Distribution of ^{137m}Ba-EDTA in dog during constant infusion. Radiograph is superimposed. A is heart blood pool. B is liver blood pool.

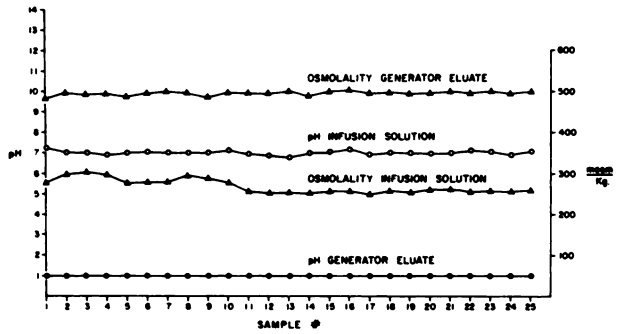

FIG. 3. pH and osmolality of generator eluate and infusion solution.

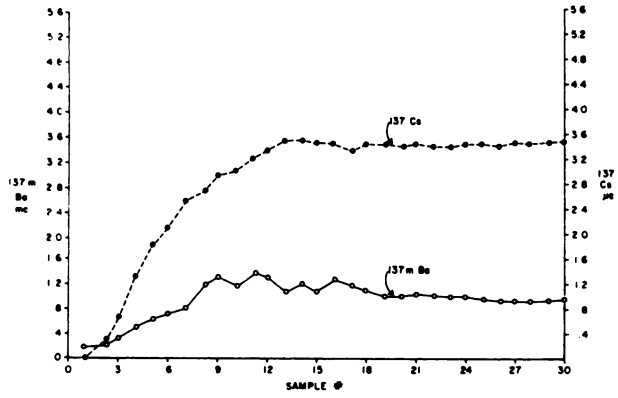

FIG. 4. ^{137m}Ba yield and ^{137}Cs contamination.

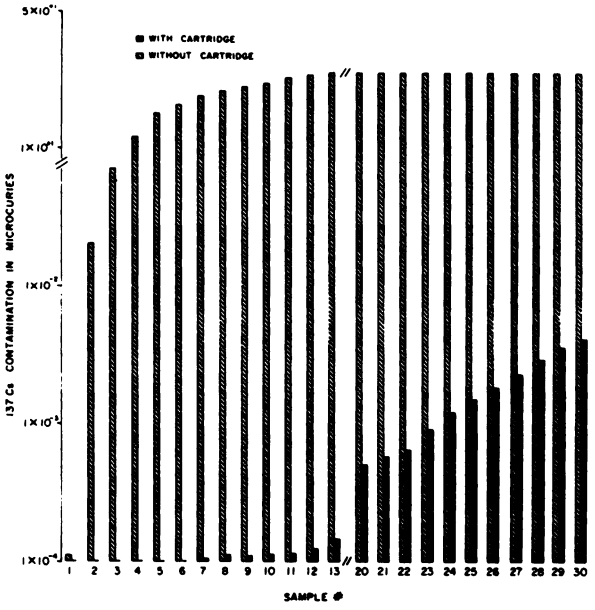

FIG. 5. ^{137}Cs contamination with and without the anti-^{137}Cs cartridge. Samples were collected over 26-min period.

RESULTS

Five millicuries of ^{137}Cs were passed over the prepared column and the eluate collected. All of the added ^{137}Cs activity was retained on the column, and the washing solution was free of any residual ^{137}Cs activity.

The generator eluate was collected (25 × 10-ml samples), and each sample was analyzed for pH and osmolality. The pH remained constant (pH = 1), and the osmolality ranged from 481 to 523 mosmols/kg (Fig. 3). Because this acidic and hypertonic solution was unsatisfactory for intravenous administration, the system was modified.

A reservoir was used where the generator eluate was collected and mixed with a chelating compound, an alkaline solution and an isotonic buffer solution. The purpose of adding EDTA was to complex the barium to maintain a constant blood level during the study. The alkaline solution was added to adjust the pH of the column eluate and the modified buffer to maintain a constant pH and osmolality throughout the infusion.

The infusate was analyzed for pH, osmolality, ^{137m}Ba yield and ^{137}Cs contamination over an infusion period of 55 min. Twenty-five 10-ml samples were collected for analysis. The pH and osmolality were observed to be within the physiological range (Fig. 3). The ^{137m}Ba yield remained at approximately 20% of generator activity per 10 ml, and the ^{137}Cs contamination approached a constant value of approximately 3.5 μCi/10 ml (Fig. 4).

A method was devised to reduce the ^{137}Cs contamination without any appreciable loss in ^{137m}Ba activity. A micro-ammonium-phospho-molybdate cartridge was developed and placed between the primary column and the reservoir. The infusate was analyzed for ^{137}Cs contamination (30 × 5-ml samples), and the results are shown in Fig. 5. Initially the ^{137}Cs contamination was undetectable but it slowly increased as the cartridge collected more cesium.

DISCUSSION

^{137m}Ba-chloride, with a 2.6-min physical half-life, has been used after a single intra-arterial injection to obtain a high photon flux for brain-tumor scanning or for blood-flow measurements (*3–5*). Intra-arterial injections are inconvenient, painful and associated with a definite, although minimal, morbidity.

To obtain a high and persistent blood level of radioactivity, a closed system was developed for the continuous intravenous administration of ^{137m}Ba-EDTA (Fig. 1). A pump was used for continuous

elution of the short-lived daughter from its long-lived parent and for the direct infusion into the subject. In this manner, high blood levels of radioactivity are conveniently obtained and, as soon as the desired measurements are completed, the delivery is stopped and the radiation exposure is terminated.

The original infusate contained approximately one maximum permissible body burden of ^{137}Cs (*8*)/150 ml—a value much too high for human administration. A method was devised to remove this contamination. This consisted of simply placing a micro-ammonium-phospho-molybdate cartridge between the generator and the reservoir. There was no decrease in ^{137m}Ba yield from the intraposition of the added ion-exchange bed. The resulting infusate was pumped through a 0.45-micron Millipore filter yielding a sterile solution suitable for human intravenous administration.

A dog was infused for 1.5 hr, representing a total barium dose of 2.9×10^{-5} μg, which is well below the toxic dose (*9*). Satisfactory definition of the cardiac blood pool was obtained in ½ hr (Fig. 2).

In humans, using a 25-mCi generator and assuming uniform distribution and no biological excretions, a 30-min infusion would result in a whole-body exposure dose of 0.0976 mR (*10*), and ^{137}Cs contamination of less than 0.5% the maximum permissible body burden of 30 μCi.

SUMMARY

A prototype infusion system was successfully developed for the continuous administration of ^{137m}Ba directly eluted from its ^{137}Cs parent. This same principle can be applied to a variety of long-lived-parent, short-lived-daughter radioisotope relationships.

ACKNOWLEDGMENT

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REFERENCES

1. STERN, H. S., MCAFEE, J. G. AND SUBRAMANIAN, G. J.: Preparation, distribution and utilization of technetium-99m sulfur colloid. *J. Nucl. Med.* **7**:665, 1966.

2. GOODWIN, D. A., STERN, H. S., WAGNER, H. N., JR. AND KRAMER, H. H.: In-113m colloid: a new radiopharmaceutical for liver scanning. *Nucleonics* **24**:No. 11, 65, 1966.

3. BLAU, M., ZIELINSKI, R. AND BENDER, M.: Ba^{137m} cow—a new short-lived isotope generator. *Nucleonics* **24**: No. 10, 90, 1966.

4. VERNEJOUL, P., DEL OLMO, J., RANGEL ABUNDES, H. AND KELLERSHOHN, C.: The importance of nuclear indicators of short half life in the study of cardiac hemodynamics. *Nucl. Med.* **5**:3, 1966.

5. VERNEJOUL, P., VALEYRE, J. AND KELLERSHOHN, C.: Dosimetry and technique for the use of ^{137m}Ba in cardiac hemodynamics. *C. R. Acad. Sci.* **264**:10, 1967.

6. VAN SMIT, R., ROBB, W. AND JACOBS, J.: Cation exchange on ammonium-molybdophosphate-I. *J. Inorgan. Nucl. Chem.* **12**:1,064, 1959.

7. SOINE, X. AND WILSON, X.: *Rogers Inorganic Pharmaceutical Chemistry,* Ch. 10, Lea and Febiger, Philadelphia, 1961.

8. Radiological Health Handbook: "Maximum permissible body burdens and maximum permissible concentrations of radionuclides in air and in water for occupational exposure." PB121784R, Revised Edition, 1960, p. 187.

9. Handbook of Toxicology, vol. 1, Acute toxicities, National Academy of Sciences, National Research Council, 1956.

10. Pamphlets 1–3. *J. Nucl. Med.* **9**:Suppl. 1, 1968.