A GENERATOR SYSTEM FOR THALLIUM-201

James A. Campbell, Ronald D. Finn and Patricia M. Smith
University of Miami School of Medicine and Baumritter Institute
of Nuclear Medicine, Mount Sinai Medical Center, Miami Beach,
Florida 33140, U.S.A.

Received June 10, 1976
Revised August 4, 1976

SUMMARY

A new and efficient method is described for the separation of ^{201}Tl from its parent ^{201}Pb. Differences in ion exchange properties facilitate the use of a generator system for this separation. The procedure itself is simple and utilizes an exchange column which retains all lead isotopes, as well as other metals, while permitting elution of carrier-free ^{201}Tl. Unlike current methods, the ^{201}Tl can be made clinically available within hours of its generation and the need for elaborate extractions is avoided.

Key Words: Ion Exchange, Thallium-201, Generator

INTRODUCTION

Among the short-lived isotopes currently under investigation as radiopharmaceuticals, thallium-201 has been shown to be a superior agent for myocardial perfusion imaging (1-6). Thallium-201, a radionuclide having a half-life of 73 hours, is a generator product obtained from its parent, lead-201. Unlike most generator systems, however, where the parent has a significantly longer half-life than the daughter, the ^{201}Pb-^{201}Tl generator exhibits a parent possessing a shorter half-life ($T_{1/2}$ = 9.4 hrs). Because the decay rate of the lead parent is greater than the rate of generation of the thallium daughter, such a generator would not be expected to provide a continuing source of the daughter isotope beyond 3-4 days.

Methods currently employed for the separation of thallium-201 from lead-201 involve elaborate ether extractions or elutions, procedural repetition for maximizing thallium yield and material losses due to time lapse while waiting for the lead-201 to decay two or more half-lives (1,7).

The present study proposes the use of a thallium generator system whereby ^{201}Pb can be directly applied to a cation exchange resin within 2-3 hours after end of bombardment of an enriched ^{203}Tl powder target. The ^{201}Tl daughter product is subsequently eluted at convenient time intervals relative to the ^{201}Pb decay. The method is simple and eliminates the need to repeat separation procedures following further decay of the lead parent. Furthermore, unlike the ether extraction procedure, the ^{201}Pb-^{201}Tl generator excludes the possibility that the thallium-201 will be contaminated with lead-203, a secondary product produced during cyclotron bombardment.

MATERIALS AND METHODS

Lead-201 is routinely produced by the ^{203}Tl(p,3n)^{201}Pb nuclear reaction on an enriched $^{203}Tl_2O_3$ powder target using an external beam of the Mount Sinai Medical Center cyclotron. The production rate (8) of ^{201}Pb is typically 10 mCi/μAH/g Tl_2O_3. Separation of the ^{201}Pb from the target material is accomplished by extraction of the thallium into isopropyl ether and subsequent elution of the aqueous lead-201 solution over a Bio-Rad Dowex AG1-X8 anion exchange resin (9). Microgram quantities of target material, still present after ether extraction, adhere to the column. The eluate, containing ^{201}Pb and ^{203}Pb (ca. 10%), is evaporated to dryness and brought up to a predetermined volume in hydrochloric acid. For this study the lead activity was redissolved in 1-2 ml of 0.005 N hydrochloric acid containing 0.1% chlorine gas. Spot tests on the product for nanogram quantities of thallium (Rhodamine B test) (10), aluminum (alizarin test) (11), and iron (potassium ferrocyanide test) (12) are performed routinely. Such contaminants could arise from the target and target holder during processing. Radioassay and radionuclidic purity are determined by multi-channel pulse height analysis utilizing a Ge(Li) detector. Following each processing, enriched thallium-203 is recovered by precipitation and conversion to the oxide.

The 1-2 ml volumes of ^{201}Pb/^{203}Pb (approximately 20-40 mCi/ml, ^{201}Pb) were applied to a pre-conditioned generator system (resin, treated with 0.005 N HCl containing 0.1% Cl_2 immediately before use) consisting of a glass column (0.7 x

10 cm), wrapped with foil, plugged at the bottom with a fritted glass disk and filled to a height of 3.0 cm with Bio-Rad AG50W-X4, minus 400 mesh, cation exchange resin in hydrogen form. The ^{201}Tl was eluted from the generator at various time intervals (shown in Tables 1 and 2) in 3-4 ml aliquots of 0.005 N HCl (ca. 0.1% Cl_2) and the radionuclidic purity determined. Oxidation state of the eluted ^{201}Tl was verified by paper chromatography (1) which differentiates Tl^{+1} and Tl^{+3}. The Tl^{+1} remains at the origin while the Tl^{+3} moves with the solvent (R_F = 0.60). Whatman No. 3 MM paper and a solvent consisting of 10% Na_2HPO_4 and 90% acetone were used. The gamma spectrum of the product, before and after generator separation, was monitored for one week to confirm the half-lives of the lead-201 and thallium-201. Resin beds, after total ^{201}Tl recovery, were studied as follows: (1) continuously eluted for one week with a total of 42.0 ml 0.1% Cl_2-0.005 N HCl to determine point of lead breakthrough; (2) eluted with 2-12 N HCl to effect ^{201}Pb/^{203}Pb recovery; and (3) removed from the glass column, quartered, dried and assayed for radionuclidic purity.

Pooled volumes of eluant (6.0 ml) were either evaporated to dryness and the thallium activity redissolved in bacteriostatic water containing 0.9% sodium chloride or neutralized with 0.1 N NaOH. At neutral pH, these solutions, containing $^{201}Tl^{+1}$ exclusively, were filtered through a sterile 0.22-micron filter into sterile vials and tested for sterility and apyrogenicity by a commercial firm.

RESULTS

A series of generator studies was conducted using varying amounts of ^{201}Pb activity (30-90 mCi). Tables 1 and 2 reveal the results of two such studies. The recorded time for each elution was that time after end of processing (EOP) of the ^{201}Pb. EOP is defined as the time at which the last drop of ^{201}Pb activity was eluted from the anion exchange resin during processing. Although only trace amounts of ^{201}Tl were present at EOP, this time was used as a point of reference and, unless otherwise indicated, all activities have been corrected to EOP. The total ^{201}Tl activity recovered from 37.0 mCi of ^{201}Pb over a 41.2 hr period (Table 1) was 6.46 mCi or 17.5% of the lead activity (^{201}Pb) applied to the column. When 88.9 mCi of ^{201}Pb was applied to a column, 14.12 mCi of ^{201}Tl was eluted which was 15.8% of the ^{201}Pb (Table 2)

TABLE 1. ELUTION OF A ^{201}Pb-^{201}Tl GENERATOR AT SHORT TIME INTERVALS*

Time, t (hr)**	^{201}Tl at Time, t (mCi)	^{201}Tl Corrected to EOP ** (mCi)	Percent Thallium-201 Eluted ***
1.5	0.54	0.56	8.7
3.0	0.76	0.79	12.2
6.0	0.94	1.00	15.5
9.0	0.70	0.77	11.9
12.0	0.62	0.70	10.8
15.0	0.47	0.54	8.4
18.0	0.30	0.36	5.6
21.0	0.32	0.39	6.0
24.0	0.26	0.33	5.1
27.0	0.20	0.26	4.0
30.0	0.16	0.21	3.2
33.0	0.13	0.18	2.9
36.0	0.12	0.17	2.6
39.0	0.07	0.10	1.2
41.2	0.07	0.10	1.2

* ^{201}Pb activity applied to this generator was 37.0 mCi.

** EOP = End of Processing for the separation of ^{201}Pb from the cyclotron target material.

*** Third column values expressed as a percent of the total eluted (6.46 mCi).

TABLE 2. ELUTION OF A ^{201}Pb-^{201}Tl GENERATOR AT LONG TIME INTERVALS

Time, t (hr)	^{201}Tl at Time, t (mCi)	^{201}Tl Corrected to EOP (mCi)
2.0	0.73	0.74
24.0	8.14	10.23
40.0	1.38	2.01
64.0	0.61	1.12

The lead activity was recovered by elution with 2N hydrochloric acid following final elution of the 41.2-hr generator (Table 1). Of 1.28 mCi of ^{203}Pb initially applied to the column, 0.92 mCi was recovered; 0.64 mCi of ^{201}Pb was also obtained. Bulk assay of the resin bed following lead recovery revealed some residual lead activity which could not be eluted using 2-12 N HCl sequentially. Radioassay of a similar resin bed after ^{201}Tl recovery (Table 2) revealed that most of the lead activity was adsorbed at the upper half of the column (Table 3). Total thallium-201 adhering to the resin was 0.67 mCi or 4.6% of the total thallium. Thus, by elution, greater than 95% of the thallium was recovered.

TABLE 3. RADIONUCLIDIC ASSAY OF RESIN FOLLOWING THALLIUM SEPARATION

RESIN SECTION*	^{201}Pb (mCi)**	^{203}Pb (mCi)**	^{201}Tl (mCi)
1st 0.75 cm	83.3	1.82	0.66
2nd 0.75 cm	5.0	0.104	0.01
3rd 0.75 cm	0.01	0.0002	0.0017
4th 0.75 cm	0.0092	0.00014	0.0016

* A 3.0 cm resin bed was quartered; the 1st section represents the column head; the 4th, its base.

** 88.9 mCi ^{201}Pb and 1.97 mCi ^{203}Pb were initially applied to the column.

A concentration of 0.005 N HCl containing 0.1% chlorine was sufficient to insure optimum elution of the ^{201}Tl activity without causing lead breakthrough. The resin beds were eluted with 14, 3-ml aliquots of 0.1% Cl_2-0.005 N HCl without ^{201}Pb/^{203}Pb appearing in the eluate. However, a chlorine-saturated (ca. 1.5%) solution of 0.005 N HCl resulted in elution of lead activity (ca. 1-2% of that applied to the column). An aliquot of pre-column material was dissolved in 0.005 N HCl containing no chlorine and allowed to decay overnight to ^{201}Tl. Paper chromatography revealed 97% Tl^{+1} and 3% Tl^{+3}. In contrast, column eluates contained 100% Tl^{+3} due to the presence of chlorine oxidant. Exposure of eluates to light over several days caused decomposition of chlorine and subsequent reduction of Tl^{+3} to the Tl^{+1} oxidation state.

Spot testing of the ^{201}Pb product prior to generator separation of ^{201}Tl revealed the presence of trace amounts of aluminum. This contaminant, arising from the target holder, was not detected in the eluates when similarly spot tested.

Generator-produced ^{201}Tl possesses a radioisotopic purity greater than 99% and, at neutral pH, was sterile and pyrogen-free after millipore filtration. The only detectable radionuclidic impurity was ^{202}Tl ($T_{1/2}$ = 12.2 d) amounting to 0.2% at thirty-six hours post EOP.

DISCUSSION

An efficient procedure for the preparation of ^{201}Tl radiopharmaceuticals has been described. The method is fast, exceptionally efficient and produces carrier-free ^{201}Tl suitable for patient use. A particular advantage of using a cation exchange column for the generation of ^{201}Tl lies not only in its ability to separate thallium from lead but from other metals such as aluminum and iron which are also retained by the column (13).

Similarities in properties of thallium and lead cause difficulties in their separation. Carobene and Vicedomini (14) employed an ion exchange resin which adsorbed thallous ion and allowed lead to pass through the column. Others (12) have shown that certain cation exchange resins will adsorb lead from a weak solution of hydrochloric acid but not retain thallic ion. In our ion exchange system, lead and thallous ion were adsorbed while thallic ion was eluted. It was thus necessary to oxidize the thallium-201 by elution of the ^{201}Pb-^{201}Tl generator with 0.005 N hydrochloric acid containing 0.1% chlorine gas. Dissolved chlorine gas was found to be a suitable oxidant and, unlike sodium hypochlorite (0.05-0.5%), facilitated greater than 95% recovery of the generated thallium. However, high concentrations (ca. 1.5%) of chlorine resulted in breakthrough of lead activity. When ^{201}Tl eluates were exposed to light for several days, all the thallium was converted to the lower oxidation state as determined by paper chromatography. Light induces decomposition of dissolved chlorine gas with subsequent reduction of thallic ion in the weakly acidic solution. Thus, it is necessary to shield the column from light during generation of ^{201}Tl to preserve the chlorine and protect thallic ion from reduction.

The data in Table 1 support the fact that thallium generation is directly proportional to the half-life of ^{201}Pb. Specifically, 50% of the total thallium yield is produced during the first 9.4 hours and can be eluted at that time in a volume as small as 3.0 ml, volume being dependent upon resin bed size. For clinical purposes, such as myocardial visualization, our system makes ^{201}Tl available to the physician within a few hours after cyclotron bombardment of the enriched thallium target material.

ACKNOWLEDGEMENTS

The authors wish to express their appreciation to Drs. Peter J. Kenny and Denny D. Watson of the Mount Sinai Medical Center for reviewing this manuscript and providing valuable comments.

REFERENCES

1. Lebowitz E., Greene M.W., Fairchild R., Bradley-Moore P.R., Atkins H.L., Ansari A.N., Richards P. and Belgrave E. - J. Nucl. Med. 16:151 (1975).

2. Bradley-Moore P.R., Lebowitz E., Greene M.W., Atkins H.L. and Ansari A.N. - J. Nucl. Med. 16:156 (1975).

3. Strauss H.W., Harrison K., Langan J.K., Lebowitz E. and Pitt B. - Circ. 51:641 (1975).

4. Ritchie J.L., Hamilton G.W., Williams D.L., English M.T. and Leibowitz E. - Circ. Supp II:231 (1975).

5. Bailey I.K., Griffith L.S.C., Strauss H.W. and Pitt G. - Am. J. Cardiol. 37:118 (1976).

6. Schelbert H., Henning H., Righetti A., Ashburn W. and O'Rourke R. - Am. J. Cardiol. 37:170 (1976).

7. Finn, J. - Personal communication, 1976.

8. Beaver J.E. - Personal communication, 1976.

9. Finn R.D., Campbell J.A., Graser C. and Smith P.M. - "A Novel Method for the Chemical Separation of Carrier-Free Thallium-201 from Enriched Thallium-203 Cyclotron Targets", presented at the First International Symposium on Radiopharmaceutical Chemistry, Brookhaven National Laboratory, Upton, Long Island, New York, September, 1976.

10. Feigl R., Anger V. and Oesper R.E. - Spot Tests in Inorganic Analysis, (6th Edition), Elsevier Publishing Co., New York, 1972, pp. 476-478.

11. Ibid., pp. 96-97.

12. Ibid., p. 269.

13. Nelson F., Murase T. and Kraus K.A. - J. Chromatog. 13:503 (1964).

14. Carobene G. and Vicedomini M. - J. Chromatog. 33:568 (1968).