THALLIUM-201 FOR MEDICAL USE. I

E. Lebowitz, M. W. Greene, R. Fairchild, P. R. Bradley-Moore, H. L. Atkins, A. N. Ansari, P. Richards, and E. Belgrave

Brookhaven National Laboratory

Thallium-201 merits evaluation for myocardial visualization, kidney studies, and tumor diagnosis because of its physical and biologic properties. A method is described for preparation of this radiopharmaceutical for human use. A critical evaluation of ^{201}Tl and other radiopharmaceuticals for myocardial visualization is given.

Thallium-201 is a potentially useful radioisotope for various medical applications including myocardial visualization and possible assessment of physiology, as a renal medullary imaging agent, and for tumor detection.

The use of radiothallium in nuclear medicine was first suggested by Kawana, et al (*1*). In terms of organ distribution (*2*) and neurophysiologic function (*3*), thallium is biologically similar to potassium. The physical–chemical explanation for the biologic similarity of Tl^+ and K^+ is that the hydrated ionic radius of Tl^+ is between K^+ and Rb^+ in size and this radius has been suggested as the property that determines passive penetration through a membrane (*4*).

These facts suggest that radiothallium should be a good potassium analog and therefore has potential for myocardial visualization and the early detection of areas of diminished perfusion and radionuclide uptake as "cold spots" (regions of decreased activity).

Presently used renal agents concentrate in the cortex; unlike these, thallium preferentially concentrates in the renal medulla (*5*). This property may be clinically useful.

The Tl^+ is taken up more by tissues in pigmented than in albino rabbits, suggesting the use of radiothallium for the diagnosis of melanoma (*6*). Because of the similarity of thallium to alkali metals such as cesium, which has been shown to concentrate in tumors (*7–9*), the use of radiothallium should also be evaluated for this application.

Thallium-201 decays by electron capture with a 73-hr half-life. It emits mercury K-x-rays of 69–83 keV in 98% abundance plus gamma rays of 135 and 167 keV in 10% total abundance. Because of its good shelf-life, photon energies, and mode of decay, ^{201}Tl was the radioisotope of thallium chosen for development.

MATERIALS AND METHODS

Thallium-201 is produced by irradiating a natural thallium target in the external beam of the 60-in. Brookhaven cyclotron with 31-MeV protons. The nuclear reaction is $^{203}Tl(p,3n)^{201}Pb$. Lead-201 has a half-life of 9.4 hr and is the parent of ^{201}Tl. The thallium target, fabricated from an ingot of 99.999% pure natural thallium metal (29.5% isotopic abundance of ^{203}Tl), is 1.3 cm in diameter and weighs 0.7 gm. The target thickness and incident proton beam energy are chosen to minimize the production of other radioisotopes of lead, which could lead to impurities in the ^{201}Tl product. After irradiation, the thallium target is dissolved in concentrated nitric acid, then evaporated to dryness. This salt is then dissolved in 50 ml of 0.025 *M* EDTA at pH 4 and passed through a Bio-Rad Dowex 50 × 8 resin column (Na^+ form, 50–100 mesh, 2.5 × 6 cm). Most of the thallium target material adheres to the column and the eluate contains radioactive ^{203}Pb and ^{201}Pb. The eluate is acidified by adding an equal volume of conc. HNO_3 and the thallium is oxidized by the addition of "Clorox." Forty micrograms of $Pb(NO_3)_2$ carrier are added to the eluate and the solution is passed through a Bio-Rad Dowex 1 × 8 resin column (H^+ form, 50–100 mesh, 2.5 × 6 cm). Thal-

Received June 10, 1974; revision accepted Sept. 23, 1974.

For reprints contact: Elliot Lebowitz, Bldg. 801, Brookhaven National Laboratory, Upton, N.Y. 11973.

lium adheres to this column and the lead activities are eluted.

This eluate containing ^{203}Pb and ^{201}Pb is allowed to stand overnight to permit the ^{201}Pb to decay into ^{201}Tl. It is then passed through another Bio-Rad Dowex 1 × 8 column to which the $^{201}Tl^{+3}$ adheres and through which the lead activities are eluted. The ^{201}Tl activity is then eluted with 20 ml of hot hydrazine-sulfate solution (20% w/v), reducing Tl^{+3} to Tl^{+1}. This Tl^{+1} eluate is evaporated to dryness twice with conc. HNO_3 and once with conc. HCl. The product is then dissolved in 5 ml of 10^{-1} *M* NaOH and the pH is adjusted to 7 by further addition of NaOH. The product is sterilized by filtration into a sterile multiinjection bottle through a 0.22-micron sterilized Millipore filter.

A Rhodamine B spot test is used to detect carrier thallium in the product before injection. The test can detect 0.02 μg of thallium. The sample tested is typically 1% of the total product; thus a negative spot test insures that less than 2 μg of thallium is present in the product. A few weeks after the ^{201}Tl is produced, a complete chemical analysis of the product is performed by emission spectroscopy.

The radiochemical purity of the product is checked by paper chromatography to differentiate Tl^{+1} and Tl^{+3}. Whatman No. 3 MM paper and a solvent 1/10 ($Na_2HPO_4 \cdot 5H_2O$) and 9/10 (acetone) are used. The Tl^{+1} stays at the origin. To demonstrate that the ^{201}Tl is not in particulate form, the product is passed through a 250 Å filter.

TABLE 1. CHEMICAL ANALYSIS OF THE ^{201}Tl PRODUCT

Element	Quantity (μg)	Element	Quantity (μg)
Tl	<2	Ni	<2
Ca	60	Al	1
B	<2	Mo	0.2
Mg	1	Cu	6
Mn	<0.2	Ag	<0.2
Si	0.2	Ti	1
Fe	1	V	1

Radionuclidic purity is analyzed by multichannel pulse-height analysis, utilizing a Ge(Li) detector. The gamma spectrum of the product is also followed for approximately 1 week to confirm the half-lives of the product and impurity gamma rays.

Product batches are tested for pyrogenicity by an

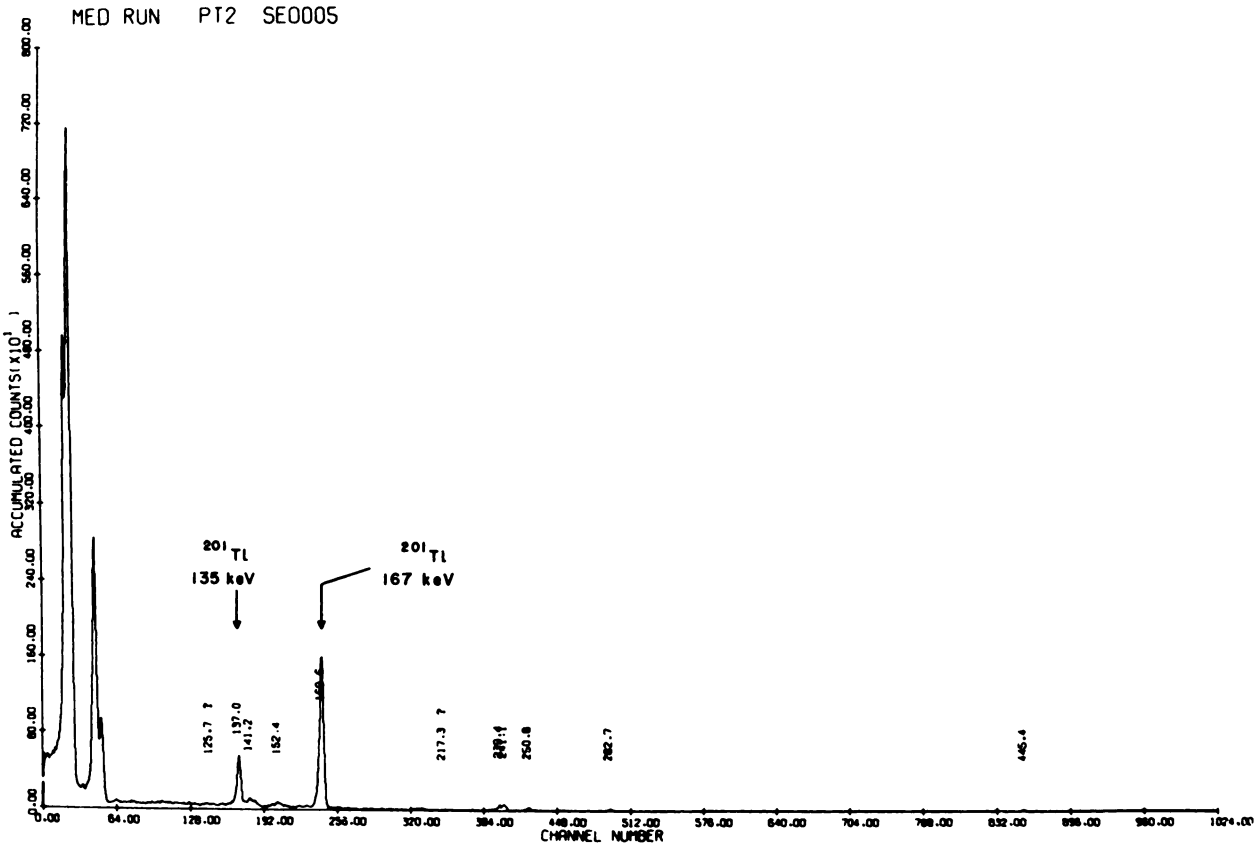

FIG. 1. Ge(Li) spectrum of ^{201}Tl product.

independent laboratory. All glassware is rendered apyrogenic by autoclaving at 180°C for 3 hr.

Measurements of the excitation function (the production cross section as a function of energy) are performed by irradiating a stack of thin (approximately 0.2 gm/cm^2) foils of thallium and analyzing the activities produced with a Ge(Li) detector. Lead-201 is determined by analysis of its 331-keV photon, which is present in 82% abundance.

RESULTS

Emission spectroscopic chemical analysis of an entire product batch is shown in Table 1. Figure 1 shows the Ge(Li) spectrum of the product, the main peaks being the x-rays and photons of ^{201}Tl. The radioisotopic purity is ≧99%, as is shown in Table 2. The product is at neutral pH, isotonic, sterile, and pyrogen-free.

The excitation function for the production of ^{201}Pb, the parent of ^{201}Tl, is seen in Fig. 2. By choosing an energy range near the peak of the excitation function, the production of ^{200}Pb and ^{202}Pb (the parents of ^{200}Tl and ^{202}Tl) radiocontaminants is minimized. With a natural thallium target, the production rate of ^{201}Tl is 0.7 mCi/μAH or correspondingly higher with an enriched ^{203}Tl target. The initial development work is being done on the Brookhaven 60-in. cyclotron but it should be possible to evaluate the production capability of ^{201}Tl in the BLIP (Brookhaven Linac Isotope Producer) using the ^{205}Tl(p,5n)^{201}Pb reaction.

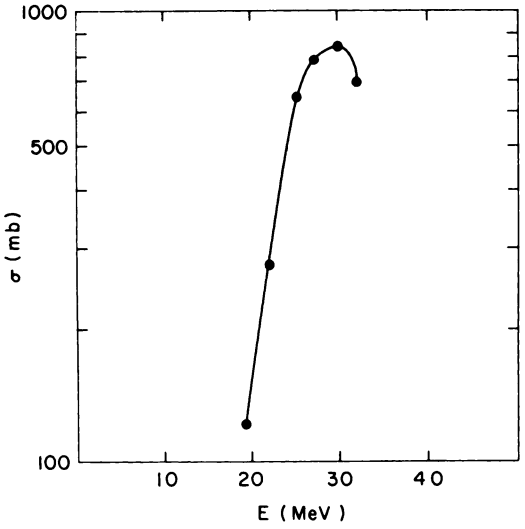

FIG. 2. ^{203}Tl(p,3n)^{201}Pb excitation function.

DISCUSSION

Using the myocardial uptake of the analogs of potassium, there are several alternatives for myocardial visualization including the radioisotopes of potassium, cesium, thallium, rubidium, and $^{13}NH_4^+$. We start by comparing the biologic behavior of K^+ and Cs^+ (*10*). Potassium is more rapidly cleared from the blood and extracted by the myocardium than is cesium. Potassium is extracted by the myocardium with 71% efficiency on a single circulation compared with 22% efficiency for cesium. Following its extraction, potassium is cleared more rapidly from the heart. Although the radioisotopes of potassium and cesium can both be used for myocardial visualization, their differences in biologic behavior are reflected in their clinical usefulness.

Advantages of potassium over cesium. First, because of its more efficient myocardial uptake and lack of recirculation, K^+ is superior for quantitative studies following intracoronary arterial injection (*10*). Second, because of its rapid blood clearance and myocardial extraction, K^+ can be used in the assessment of patients with transient myocardial ischemia (e.g., angina pectoris) by visualizing the myocardium before and after stress (*11,12*).

Disadvantage of potassium. The rapid leakage of potassium from the myocardium constitutes a disadvantage due to the inability to visualize the myocardium with potassium after the first hour postinjection (*11*), compared with the ability to use cesium for this purpose for several hours (*10,13*).

Since Tl^+ is a good biologic analog of potassium, it should have the biologic advantages of K^+ listed earlier. Furthermore, Harper has observed that the thallium activity remained in the myocardium even 18 hr postinjection in the one patient they scanned

TABLE 2. RADIOISOTOPIC ANALYSIS OF ^{201}Tl PRODUCT

Isotope	$t_{1/2}$	At time of preparation (%)	18 hr later (%)	73 hr later	146 hr later
^{200}Pb	52 hr	1.6×10^{-2}	1.5×10^{-2}	1.2×10^{-2}	9.0×10^{-3}
^{200}Tl	26 hr	1.3×10^{-1}	9.0×10^{-2}	3.7×10^{-2}	1.1×10^{-2}
^{202}Tl	12.2 days	1.2×10^{-1}	1.4×10^{-1}	2.0×10^{-1}	3.4×10^{-1}

TABLE 3. RADIOISOTOPES FOR MYOCARDIAL VISUALIZATION

Radionuclide and half-life	Photon energy (keV) and abundance	Whole-body radiation dose (rad/mCi)	Comments*
$^{13}NH_4^+$ (16) 10 min	511 200%	0.005	
^{81}Rb (17) 4.7 hr	511 67%	0.10	(1)
^{131}Cs (18) 9.7 days	29 88%	0.21	(2)
^{134m}Cs (19) 2.9 hr	128 14%	0.24	(3)
^{82}Rb (20,21) 75 sec	511 192%	~0.001	(4)
^{43}K (22) 22 hr	380 103%	0.7	
^{129}Cs (23,24) 32 hr	375 45%	0.17	
^{201}Tl 73 hr	167 (8%) 135 (2%) 69–83 (98%)	0.07	(5)
^{199}Tl 7.4 hr	455 16%	0.046	
^{123}I (and ^{131}I)— fatty acids 13 hr (25–28)	159 83%		(6)
^{11}C-norepinephrine 20 min (29)	511 200%	0.01	(6), (7)

* (1) Efforts are underway in a number of laboratories to also utilize the 13-sec ^{81m}Kr daughter of ^{81}Rb to measure regional myocardial blood flow.

(2) This energy is undesirably low for in vivo visualization of the myocardium.

(3) Contamination with long-lived ^{134}Cs is a limiting factor in the shelf-life and use of ^{134m}Cs because of the increasing patient radiation dose with shelf-time. Chandra, et al also mention the suitability of ^{201}Tl for myocardial imaging.

(4) This daughter of 25-day ^{82}Sr is under evaluation. Imaging is difficult in the short time interval between the time the blood pool is cleared of activity and the time the physical decay of ^{82}Rb has reduced its activity to an insufficient level.

(5) A good shelf-life is convenient as well as being invaluable for availability in emergency use. Using the Anger camera and low-energy collimation, ^{201}Tl should give more counts/whole-body radiation dose than any of the other potassium analogs (except for ^{82}Rb, $^{13}NH_4^+$), with at least as good resolution.

(6) Under evaluation.

(7) A more complete discussion of Table 3 can be found in BNL 18943 (1974).

with a mixture of thallium isotopes (*14*). If confirmed, this removes the disadvantage (*3*) of potassium from thallium. The ability to take many views may be crucial if it is necessary to view small infarcts in profile in order to visualize them and delayed scans may yield improved resolution.

Rubidium is a good analog of potassium (*15*) and it is expected to be almost as good an analog as thallium since the hydrated ionic radius of thallium is between potassium and rubidium.

The metabolic behavior of $^{13}NH_3$ is sufficiently complex so that diagnosis with it has been difficult to date (*16*).

Table 3 compares radioisotopes for myocardial visualization. An important new development is the use of ^{99m}Tc-complexes for visualization of necrotic tissue as a "hot spot" (region of increased uptake) (*30,31*). The combined use of ^{201}Tl and an agent such as ^{99m}Tc-tetracycline may greatly enhance the value of cardiac diagnosis by nuclear medical techniques. Thallium-201 might demonstrate the size and location of regions of ischemia and necrosis whereas ^{99m}Tc-tetracycline might perform the differential diagnosis between ischemic and necrotic regions by demonstrating only regions that are necrotic.

As is essential, our production method yields ^{201}Tl in high chemical, radiochemical, and radioisotopic purity and with high specific activity. The chemical purity demonstrated in Table 1 allows the material to be clinically suitable. The presence of <2 μg of carrier thallium in the entire product, which is insured both by the reproducibility of the chemical separation and by a spot test of the product, is 4,000 times less than the dose at which some toxic effects first appear in humans and 100,000 times less than the lowest fatal dose (*32*).

The radioisotopic purity shown in Table 2 insures that the effects of high-energy photons and long-lived impurities are negligible. These would degrade the image obtained and increase the patient radiation dose.

ACKNOWLEDGMENTS

The authors gratefully acknowledge valuable conversations with P. V. Harper, H. W. Strauss, T. Budinger, J. McAfee, W. L. Ashburn, and R. A. Moyer. The authors also acknowledge the assistance of C. Baker and the staff of the Brookhaven 60-in. cyclotron in carrying out the cyclotron irradiations. This work was supported by and performed under the auspices of the United States Atomic Energy Commission.

REFERENCES

1. KAWANA M, KRIZEK H, PORTER J, et al: Use of ^{199}Tl as a potassium analog in scanning. *J Nucl Med* 11: 333, 1970

2. GEHRING PJ, HAMMOND PB: The interrelationship between thallium and potassium in animals. *J Pharmacol Exp Ther* 55: 187–201, 1967

3. MULLINS LJ, MOORE RD: The movement of thallium ions in muscle. *J Gen Physiol* 43: 759–773, 1960

4. KORTÜM FA, BOCKRIS JO: *Textbook of Electrochemistry*, vol 2, Amsterdam, Elsevier, 1951, p 701

5. RAYNAUD C, COMAR D, BUISSON M, et al: Radioac-

tive thallium: A new agent for scans of the renal medulla. In *Radionuclides in Nephrology*, Blaufox MD, Funck-Brentano JL, eds, New York, Grune & Stratton, 1972, pp 289–294

6. POTTS AM, AU PC: Thallous ion and the eye. *Invest Ophthal* 10: 925–931, 1971

7. CHARKES ND, SKLAROFF DM, GERSOHN-COHEN J, et al: Tumor scanning with radioactive 131-cesium. *J Nucl Med* 6: 300–306, 1965

8. MURRAY IPC, STEWART RDH, INDYK JS: Thyroid scanning with 131-Cs. *Br Med J* 4: 653–656, 1970

9. NISHIYAMA H, SODD VJ, AUGUST L, et al: Tumor scanning agent: reappraisal of cesium, 129-CsCl. *J Nucl Med* 14: 635, 1973

10. POE ND: Comparative myocardial uptake and clearance characteristics of potassium and cesium. *J Nucl Med* 13: 557–560, 1972

11. STRAUSS HW, ZARET BL, MARTIN ND, et al: Noninvasive evaluation of regional myocardial perfusion with Potassium 43. *Radiology* 108: 85–90, 1973

12. ZARET BL, STENSON RE, MARTIN ND, et al: Potassium-43 myocardial perfusion scanning for the noninvasive evaluation of patients with false-positive exercise tests. *Circulation* 48: 1234–1241, 1973

13. ROMHILT DW, ADOLPH RJ, SODD VJ, et al: Cesium-129 myocardial scintigraphy to detect myocardial infarction. *Circulation* 48: 1242–1251, 1973

14. HARPER PV, Private communication, 1972

15. LOVE WD, ISHIHARA Y, LYON LD, et al: Differences in the relationships between coronary blood flow and myocardial clearance of isotopes of potassium, rubidium and cesium. *Am. Heart J* 76: 353–355, 1968

16. HARPER PV, AL-SADIR J, MAYORGA A, et al: Demonstration of myocardial ischemia in images produced with intravenous 13-NH_3. Presented at the 20th Annual Meeting of the Society of Nuclear Medicine, June 1973

17. BUDINGER TF, YANO Y, MCRAE J: Rubidium-81 used as a myocardial agent. LBL-2157, 1973

18. CARR EA, GLEASON G, SHAW J, et al: The direct diagnosis of myocardial infarction by photoscanning after administration of cesium-131. *Am Heart J* 68: 627–636, 1964

19. CHANDRA R, BRAUNSTEIN P, STREULI F, et al: ^{134m}Cs, a new myocardial imaging agent. *J Nucl Med* 14: 243–245, 1973

20. YANO Y, ANGER HO: Visualization of heart and kidneys in animals with ultrashort-lived ^{82}Rb and the positron scintillation camera. *J Nucl Med* 9: 412–415, 1968

21. BUDINGER T: Private communication, 1974

22. HURLEY PJ, COOPER M, REBA RC, et al: ^{43}KCl: A new radiopharmaceutical for imaging the heart. *J Nucl Med* 12: 516–619, 1971

23. YANO Y, VAN DYKE D, BUDINGER TF, et al: Myocardial uptake studies with ^{129}Cs and the scintillation camera. *J Nucl Med* 11: 663–668, 1970

24. FELLER PA, KEREIAKES JG: Dosimetry of ^{129}Cs—Further comments. *Phys Med Biol* 19: 220–221, 1973

25. EVANS JR, GUNTON RW, BAKER RG, et al: Use of radioiodinated fatty acid for photoscans of the heart. *Circulation Res* 16: 1–10, 1965

26. GUNTON RW, EVANS JR, BAKER RG, et al: Demonstration of myocardial infarction by photoscans of the heart in man. *Am J Cardiol* 16: 482–487, 1965

27. BONTE FJ, GRAHAM KD, MOORE JG: Experimental myocardial imaging with 131-I-labeled oleic acid. *Radiology* 108: 195–196, 1973

28. POE ND, ROBINSON GD, MACDONALD NS: Myocardial extraction of variously labeled fatty acids and carboxylates. *J Nucl Med* 14: 440, 1973

29. ANSARI AN, ATKINS HL, CHRISTMAN DR, et al: ^{11}C-Norepinephrine as a potential myocardial scanning agent. *J Nucl Med* 14: 619, 1973

30. HOLMAN BL, DEWANJEE MK, IDOINE J, et al: Detection and localization of experimental myocardial infarction with ^{99m}Tc-Tetracycline. *J Nucl Med* 14: 595–599, 1973

31. BONTE FJ, PARKEY RW, GRAHAM KD, et al: A new method for radionuclide imaging of myocardial infarcts. *Radiology* 110: 473–474, 1974

32. THINES CH, HALEY TJ: *Clinical Toxicology*. Philadelphia, Lea and Febiger, 1964, p 295