Production of 7.6-Minute Potassium-38 for Medical Use

Roy S. Tilbury, William G. Myers, Ramesh Chandra, J. Robert Dahl, and Richard Lee

Memorial Sloan-Kettering Cancer Center, New York, New York

A method is described for generating 20–30 mCi of 7.6-min potassium-38 by means of a small cyclotron. Sodium chloride is mounted on a water-cooled tantalum plate, by evaporation from an aqueous solution. It is bombarded with 14.7-MeV helium-4 ions, at 50 μA. The K-38 is produced free of other radionuclides. For intravenous injection the bombarded NaCl is dissolved in sufficient pyrogen-free water to make an isotonic saline solution, which then is sterilized by filtration. Other methods of production investigated were the bombardment of: carbon tetrachloride with He-4 ions; calcium oxide with 7.8-MeV deuterons; and potassium chloride with 23-MeV He-3 ions. These gave products that were unsuitable for clinical applications. Chiefly because of the short half-life of K-38, the whole-body radiation exposure is estimated to be only about 12 mrad/mCi, and exposures to the heart and kidneys are approximately ten times greater.

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Potassium-38 interests us (*1*) principally for potential applications for myocardial imaging and as a radioindicator for studies involving the rapid turnover of "new" potassium (*2*) in other organs or tumors. Its 7.613-min half-life (*3*) with low radiation exposures permits studies to be performed repeatedly to follow the course of disease or of changes induced physiologically or pharmacologically. Since K-38 is a positron emitter, positron tomography may be used to determine the loci of accumulations of "new" potassium (*2*).

We present our results on methods for the generation, by means of a small cyclotron,* of multimillicurie amounts of K-38 for medical use (Table 1) (*4,5*).

Lambrecht et al. (*6*) recently have reported the production of K-38 in the $^{40}Ar(p,3n)^{38}K$ nuclear reaction by bombarding argon gas with 32-MeV protons. The Q value of −23.2 MeV (*5*) precludes the use of this method with a small cyclotron.

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For reprints contact: Roy S. Tilbury, Biophysics Laboratory, Memorial Sloan-Kettering Cancer Ctr., 1275 York Ave., New York, NY 10021.

METHODS AND RESULTS

Production of potassium-38. Details of the cyclotron facility at The Sloan-Kettering Institute for Cancer Research were described previously (*7,8*).

The amounts of K-38 were assayed with a standard well ionization chamber. The radionuclidic purity was assessed with a Ge(Li) gamma ray spectrometer, and with a G-M detector for pure β^- emitters, none of which were found.

I. $^{35}Cl(^4He,n)^{38}K$ nuclear reaction. One of the targets used by Hurst and Walke in their discovery of K-38 in 1937 (*9*) was chlorine, as either lithium or sodium chloride. A strong radioactivity was induced by the $^{35}Cl(^4He,n)^{38}K$ nuclear reaction when these targets were bombarded with 11-MeV He-4 ions. Chlorine-35 comprises 75.77% of natural chlorine, and the remainder is chlorine-37 (*3*).

Ia. Chlorine target, as sodium chloride. The simplest method, giving the best yields of K-38, involved bombardment of sodium chloride with 50 μA of 14.7-MeV helium-4 ions. One hundred milligrams of NaCl were deposited on a heated tantalum target-holder plate by

TABLE 1. GENERATION OF POTASSIUM-38 WITH A SMALL MEDICAL CYCLOTRON

Target	Nuclear reaction	Yield mCi/μA at saturation	Impurities	Comments
NaCl (solid)	$^{35}Cl(^{4}He,n)^{38}K$	0.4–1.0 (aver. = 0.6)	None found	No chemistry, high yield
CCl_4 (liquid)	$^{35}Cl(^{4}He,n)^{38}K$	0.2–0.8	None found	Chemistry required, high yield
CaO (solid)	$^{40}Ca(d,^{4}He)^{38}K$	0.28	^{43}Sc small amount	Chemistry required, low yield
KCl (solid)	$^{39}K(^{3}He,^{4}He)^{38}K$ and $^{37}Cl(^{3}He,2n)^{38}K$	0.12	^{43}Sc small amount; ^{34m}Cl large amount	Chemistry required, much carrier K, very low yield

slowly evaporating an aqueous solution of reagent-grade sodium chloride. The target had an elliptical shape with axes about 2 × 4 cm, and the He-4 beam struck the target at an angle of 30° to the long axis, thereby doubling the effective thickness of the target (Fig. 1). Tantalum was chosen to support the target because it was found to be inert to molten sodium chloride when heated in helium to 850° for 30 min. Nickel, stainless steel, "Havar," and copper reacted with NaCl under these conditions. The target is held in place under vacuum at the end of the cyclotron's external beam tube. After irradiation, the bombarded NaCl containing about 50 ppm of potassium is washed off the tantalum plate with 10 ml of pyrogen-free water. This forms a nearly isotonic saline solution containing ionic K-38. After sterilization by passing through a 0.22-μm Millipore filter, the solution (pH 6.5) is ready for injection. The product from five batches was tested and found to be sterile and pyrogen-free.

At the end of a 15-min bombardment with 50 μA of He-4 ions, 20–30 mCi of K-38 are generated, and 10–15 mCi are available in injectable form. The average yield for 21 production runs was 0.58 ± 0.17 mCi/μA at the end of a saturation bombardment. When a thick target of compressed NaCl was bombarded at a beam current of only 1 μA, the saturation yield was 1.5 mCi/μA.

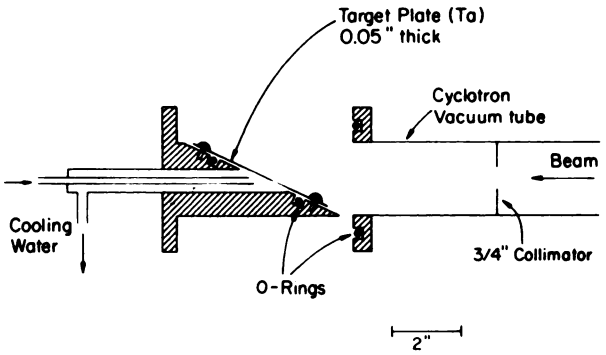

FIG. 1. Water-cooled target system used in production of K-38. About 100 mg of NaCl is deposited by slow evaporation on tantalum target plate in elliptical shape (axes 3.8 and 1.9 cm).

No radioactive contaminants have been detected, although one might expect that minute amounts of Ar-37, K-40, Al-26, and Cl-34m might be present (see Table 2). The energy of the He-4 ions is too low to produce undesirable radioactivity from the target's medium-Z supporting material. The radioactivity of the K-38 product followed an exponential decay with a half-life of 7.7 ± 0.1 min over a 58-min period.

The product was tested for the presence of hypochlorite with lead acetate paper, and for chlorate with $MnSO_4$-H_3PO_4; the negative results indicated <10 μg/ml.

Ib. Chlorine target as carbon tetrachloride. Liquid CCl_4 was bombarded with the He-4 ions, which penetrated thin metal-foil windows into a liquid-target chamber. Radiolysis released chlorine, which corroded the metal windows. "Havar" foils, 1.3×10^{-3} cm thick, and titanium or nickel foils twice as thick, all failed to withstand the corrosion for more than two bombardments.

Tantalum foil, 2.5×10^{-3} cm thick, was not attacked significantly, but the yields of K-38 were low because the thick foil absorbed much of the He-4 beam. We are exploring the feasibility of developing a flowing CCl_4 target to generate K-38 continuously.

Separation of K-38 from the bombarded CCl_4 targets, batchwise, merely required shaking the CCl_4 with about 10 ml of 0.1 *N* HCl in a separatory funnel. Potassium-38 passed into the aqueous phase, which was separated and rapidly evaporated to dryness. The K-38 was then taken up in normal saline solution, which was passed through a 0.22-μm Millipore filter.

II. $^{40}Ca(d,^{4}He)^{38}K$ nuclear reaction. Hurst and Walke (*9*) bombarded calcium metal with 5.5-MeV deuterons and were able to separate K-38, which was contaminated with radioactive scandium. We tried calcium oxide and 7.8-MeV deuterons, and ran into the same problem (Table 1). At this energy, moreover, the cross section for K-38 is only a few millibarns (*10*), and the yield is low.

III. $^{39}K(^{3}He,^{4}He)^{38}K$ and $^{37}Cl(^{3}He,2n)^{38}K$ reac-

TABLE 2. ENERGETICS OF He-4 NUCLEAR REACTIONS WITH NaCl

Target nuclide	Nuclear reaction	Product	Half-life	Q value (MeV)	E_{min}* (MeV)
Cl-35	^{4}He;n	K-38	7.6 min	− 5.88	6.55
	^{4}He;d	Ar-37	34 day	− 8.77	9.77
	^{4}He;^{4}He,n	Cl-34m	32 min	−12.63	14.07
	^{4}He;2n	K-37	1.2 sec	−17.93	—
Cl-37	^{4}He;n	K-40	10^9 yr	− 3.88	4.30
	^{4}He;2n	K-39	Stable	−11.68	—
Na-23	^{4}He;n	Al-26	7×10^5 yr	− 2.96	3.47
	^{4}He;2n	Al-25	7.2 sec	−14.31	—
	^{4}He;^{4}He,n	Na-22	2.6 yr	−12.42	14.58

* Where E_{min} = Q value (mass of compound nucleus/mass of target).

tions. When solid potassium chloride was bombarded with 23-MeV He-3 ions, the yield of K-38 was only 0.12 mCi/μA at saturation, and the residue of stable potassium raised the toxicity beyond tolerance. Furthermore, contaminating Cl-34m and Sc-43 would necessitate a chemical separation (Table 1).

Potassium-38 studies in animals. Using several NaCl targets, we were able to carry out a series of scans of a pentobarbitalized rhesus monkey at 8, 15, and 30 min after injection of a solution of K-38 intravenously, and to repeat such a series at hourly intervals. A dual-head rectilinear scanner for high-energy photons was used to make the images (*11*).

The heart was visualized well in all three images in each series, although the best contrast was obtained in the first image (Fig. 2). Potassium-38 also accumulated rapidly in the liver, spleen, gut, kidneys, and lower part of the head (possibly the salivary glands). The effects of several drugs upon the uptake of K-38 by the myocardium are under study and are being reported separately (*12*).

Temporal clearance rates in the heart and liver of a dog (Fig. 3) were determined with a computerized gamma camera. Both organs showed rapid uptakes of the K-38 from the blood. The K-38 was retained without significant loss for 2–10 min after the i.v. injection. Poe showed that K-42 remained at plateau level in the heart from 5 to 20 min, then cleared with a half-time of 6.5 hr (*13*).

CONCLUSIONS

Potassium-38 is generated readily by bombarding

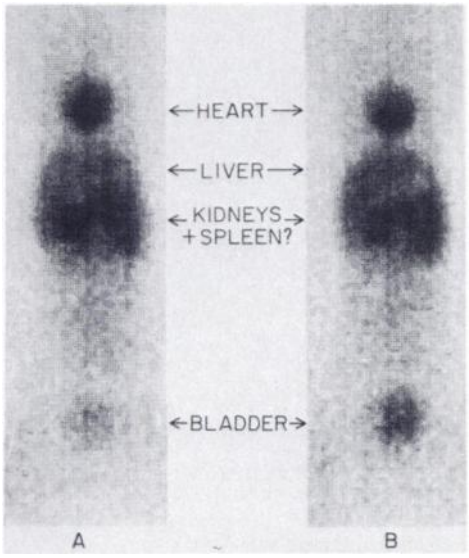

FIG. 2. Sequential rectilinear scans of rhesus monkey. (A) 8–33 min; (B) 15–40 min after injection of 8 and 9.5 mCi, respectively of K-38 in saline. Both scans are anterior views; left side of monkey at right of figure. Gray-scale display consists of 20 equally spaced levels, corrected for decay to start of scan.

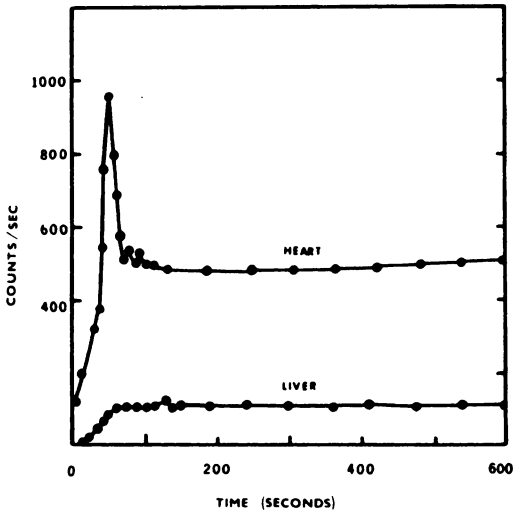

FIG. 3. Radioactivity in heart and liver regions as function of time following K-38 administration to anesthetized dog. Dynamic data were recorded and displayed using gamma-camera system; regions of interest circumscribing heart and liver were defined and integrated count rate, corrected for nuclear decay, was computed for appropriate time intervals.

TABLE 3. RADIATION PARAMETERS FOR K-38 ($T_{1/2}$ = 7.6 MIN)

Radiation (i)	Mean no. per disintegration (N_i)	Mean energy per particle E_i (MeV)	Equilibrium dose constant Δ_i (g-rad/μCi-hr)
Positron	0.99	1.142	2.408
Gamma 1	1.00	2.170	4.622
Annihilation	1.98	0.511	2.155

chlorine, in the form of NaCl or CCl_4, with 14.7-MeV He-4 ions furnished by a small medical cyclotron. The 20–30 mCi amounts produced are adequate for applications of K-38 experimentally or clinically. The K-38 is free of radioactive impurities.

When K-38 ions in solution are injected intravenously, they accumulate in the myocardium within minutes, and images of the heart are obtainable from the 511-keV radiation. The K-38 also is taken up rapidly in the liver, spleen, and lower part of the head.

The 7.6-min half-life of K-38 permits frequently repeated assays in assessments of physiological or pharmacological effects on potassium metabolism.

The short half-life also results in low radiation exposure (see Appendix).

FOOTNOTE

* Model CS-15, Cyclotron Corp.

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Dr. Myers is a Visiting Professor from the Dept. of Radiology, The Ohio State Univ. Hospitals, 410 W. 10th Ave., Columbus, OH 43210.

Dr. Chandra is on sabbatical leave from New York Univ. Medical Ctr., 560 First Ave., New York, NY 10016.

APPENDIX

Radiation absorbed dose estimates for potassium-38. In these calculations, the absorbed-fraction method was followed, as outlined by Loevinger and Berman (*14*) and modified by Cloutier et al. (*15*). Nuclear data were taken from the Table of Isotopes (*3*) and are given in Table 3, together with the calculated values of the equilibrium dose constants, Δi, which are needed in these calculations. The absorbed fractions for the two gamma photons and the various target-to-source combinations were either obtained directly from Snyder et al. (*16*) or calculated from that reference using the reciprocity theorem. These are given in Table 4. Since biological distribution data in humans are not currently available, the data obtained in rats by Gehring and Hammond (*17*) were used. To be conservative, we assumed that the maximum uptake of K-38 occurs in each organ at 2 min after injection and that no biological excretion occurs after that time. Extrapolation of rat data for the calculation of radiation doses to human organs was done as by Feller and Sodd (*18*). The calculated cumulative radioactivities for human organs are given in Table 5. The results of the radiation dose calculations are given in Table 6.

Since the kidneys and the heart are the organs with the two highest relative concentrations, radiation doses to these organs were calculated and included contributions from the radionuclide distributed in other organs. Radiation dose to the total body was calculated assuming a uniform distribution of radionuclide. Because of the higher radiation sensitivity of the testes and bone marrow, we have also estimated the radiation absorbed dose to these organs. Since the radiopotassium concentration in the testes is one fifth of the average concentration in the total body (*17*), the

TABLE 4. ABSORBED FRACTIONS NEEDED IN RADIATION DOSE CALCULATIONS

Source	ϕ_i (Kidney-source)		ϕ_i (Heart-source)	
	Gamma 1	Annihilation	Gamma 1	Annihilation
Heart	0.0009	0.0010	0.096	0.12
Kidneys	0.056	0.073	0.0018	0.0021
Liver	0.0030	0.0038	0.0039	0.0057
Lung	0.0009	0.0012	0.0094	0.011
Intestine	0.0026	0.0027	0.0006	0.0007
Remainder of body	0.0013	0.0010	0.0024	0.0026
	ϕ_1 (T.B.*–T.B.) = 0.284		ϕ_2 (T.B.–T.B.) = 0.340	

* T.B. = total body.

TABLE 5. CUMULATED RADIOACTIVITY PER mCi OF K-38 IN VARIOUS ORGANS AFTER I.V. ADMINISTRATION

Organ	$\tilde{A}_r$ (μCi − hr)
Kidneys	7.39
Intestine	8.50
Heart	9.05
Lung	5.54
Muscle and plasma	64.9
Liver	4.80
Total	184.8

TABLE 6. RADIATION DOSE ESTIMATES FOR I.V. ADMINISTRATION OF K-38

Organ	Dose (mrad/mCi)
Total body	12
Heart	49
Kidneys	75
Bone marrow	<10
Testes	<10

radiation absorbed dose to the testes was estimated to be less than the sum of the gamma-ray portion of the total-body dose plus that due to positron emissions in the organ itself. Although no radionuclide concentration data are given by Gehring and Hammond for bone marrow, the prompt uptake of potassium in this organ should similarly be low, and the absorbed dose to bone marrow is therefore estimated to be the same as in the testes.

In the absence of human distribution data, the estimates in Table 6 may serve usefully only as a guide for the administration of K-38 to humans. These radiation dose estimates differ significantly from those of Lambrecht et al. (*6*) but Christman and Lambrecht from that group kindly recalculated the dose estimates and found them to agree with those reported here (personal communication).

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ABSTRACTS: SOCIETY OF NUCLEAR MEDICINE 27th ANNUAL MEETING

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