Human Biodistribution and Dosimetry of the PET Perfusion Agent Copper-62-PTSM

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Copper-62-pyruvaldehyde bis(N^4-methyl)thiosemicarbazone (PTSM) has been proposed as a generator-produced radiopharmaceutical for perfusion imaging using PET. Several clinical studies have demonstrated the ability of ^{62}Cu-PTSM to quantitate myocardial and cerebral perfusion in humans. Because ^{62}Cu-PTSM is generator-produced, it can be provided to clinical centers without cyclotron availability and, therefore, represents a cost-effective, practical PET perfusion tracer for clinical applications. To assess the safety, time-dependent biodistribution, and whole-body and organ-specific absorbed radiation dose estimates of this tracer, a Phase I study of ^{62}Cu-PTSM was performed using whole-body imaging with PET in 10 healthy volunteers and with the radiopharmaceutical delivered by a compact modular generator unit. **Methods:** Five male and five female subjects underwent a series of clinical tests and head-to-midthigh, whole-body PET scans at three time points over 1 hr after intravenous injection of ^{62}Cu-PTSM. Before injection of the tracer, PET transmission scans were performed and used to correct the emission data for attenuation. Final image data were expressed in units of mCi/cc. Using standard organ weights, the percent injected dose per organ was calculated. Biodistribution data were obtained at three different time points and from these data biological half-lives in different organs were determined for calculation of radiation absorbed dose estimates. **Results:** The liver was seen as the critical organ receiving a dose of 0.0886 rad/mCi. This organ defined the maximum single injected dose at 56 mCi using the limit of 5 rads to a critical organ per study per year. The whole-body dose is 0.0111 rad/mCi, resulting in a 0.622 rad exposure with a maximum single injection dose. Only trace levels of activity were found in the urine, which suggests low levels of urinary excretion and bladder exposure. No significant clinical, electrocardiographic or laboratory abnormalities were seen after the injection of ^{62}Cu-PTSM. **Conclusion:** Copper-62-PTSM is a clinically safe radiopharmaceutical with favorable dosimetry for human studies at injected doses significantly above those projected for use in clinical studies.

Key Words: PET, copper-62-pyruvaldehyde bis(N^4-methyl)thiosemicarbazone, dosimetry

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Generator-produced ^{62}Cu is attractive for use in diagnostic imaging with PET (*1–5*). The advantages of the ^{62}Zn/^{62}Cu generator system are the favorable half-life of the daughter ^{62}Cu ($t_{1/2}$ = 9.76 min) with 100% positron decay and the large production yields of the ^{62}Zn parent isotope with medium-energy cyclotrons.

Several studies have demonstrated the potential of ^{62}Cu-pyruvaldehyde bis(N^4-methyl)thiosemicarbazone (PTSM) as a generator-produced PET perfusion tracer (*6–8*). Copper-62-PTSM demonstrated a high, first-pass extraction along with prolonged tissue retention and rapid clearance from the blood pool, suggesting the ability of ^{62}Cu-PTSM to quantitate blood flow in organs such as the heart, brain and kidney (*9–12*). Initial human studies have shown prolonged myocardial retention, as well as favorable myocardial-to-blood pool and myocardial-to-lung ratios (*13,14*). Comparisons of ^{62}Cu-PTSM to $^{13}NH_3$ and ^{15}O-water have demonstrated similar estimates of myocardial perfusion at resting flows but decreased correlation at hyperemic flows (*14–16*). One of the reasons for the decline in uptake at hyperemic blood flow may be the binding of copper-PTSM to serum albumin, which limits tissue extraction at high flows (*16*).

Although the rapid uptake and time dependent retention of ^{62}Cu-PTSM in human myocardium (clearance half-time of 105 min) and similar rapid uptake and prolonged retention in the brain has been demonstrated (*13,17*), the time dependent distribution in other organs has not been reported. The purpose of this study was to evaluate the safety, time-dependent biodistribution and dosimetry of ^{62}Cu-PTSM in normal human volunteers using a commercially produced, modular ^{62}Zn/^{62}Cu generator system.

MATERIALS AND METHODS

Zinc-62/Copper-62 Generator and Copper-62-PTSM Production

These studies used a compact, modular ^{62}Zn/^{62}Cu generator equipped for direct delivery of the ^{62}Cu-PTSM radiopharmaceutical. The generator consistently delivered the ^{62}Cu-daughter in >90% yield with <0.1 μCi ^{62}Zn breakthrough per elution in generators constructed to deliver clinically useful levels of ^{62}Cu (35 mCi) after shipment. The ^{62}Zn/^{62}Cu generator was prepared at Proportional Technologies, Inc. (Houston, TX) and shipped to the University of Wisconsin PET Center (*18,19*). The ^{62}Zn/^{62}Cu generator is packaged in a rugged aluminum housing for safe shipment (Fig. 1). The internal configuration of the modular generator system, equipped to directly deliver ^{62}Cu-PTSM at the generator outlet, is illustrated in Figure 2. The $^{62}Cu^{2+}$ion is selectively eluted from the shielded generator column in 0.2 *M* HCl:1.8 *M* NaCl using a peristaltic pump to regulate the rate of elution. A second channel on the peristaltic pump is used to mix the acidic eluate with two equivalents of a sterile aqueous sodium acetate (NaOAc) at the column outlet. A third peristaltic pump channel then delivers an ethanol solution of the bis(thiosemicarbazone) ligand into the acetate-buffered eluate stream, resulting in essentially quantitative formation of the ^{62}Cu-bis(thiosemicarbazone) radiopharmaceutical before the eluate reaches the outlet of the generator housing. A push button automated pump provides delivery of eluant. In a single, 33-sec elution, the generator produces a 5-ml sterile, pyrogen-free, acetate-buffered solution containing 0.4% EtOH and up to 50 mCi of ^{62}Cu. This solution is diluted to isotonic levels by preloading the receiving syringe with 28 ml of sterile water, providing a solution ready for intravenous

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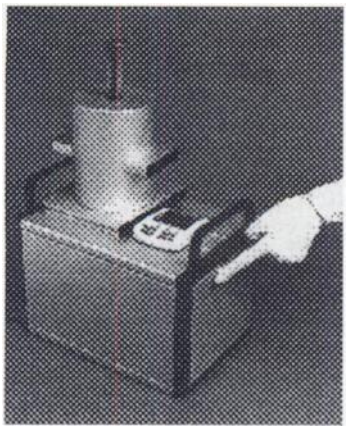

FIGURE 1. Generator for production of doses of ^{62}Cu-PTSM tracer.

administration. Before shipping, sterility tests were performed by inoculation on tryptic soy broth (TSB) and thioglycolate medium. Pyrogen tests were performed by a limulus lysate test and tested negative at 2eu/ml. Radiochemical chemical purity was tested by thin-layer chromatography (TLC). Radioisotopic and chemical purity were assessed by high-purity germanium spectra at 30 min and 3 hr postelution. The 30-min spectrum provided identification of the ^{62}Cu isotope. The gamma spectrum of the eluate was collected after 3-hr decay to determine the level of radionuclidic contaminants: ^{62}Zn breakthrough (597 keV gamma) and ^{61}Cu (656 keV gamma). The results of sterility and pyrogenicity testing were negative and breakthrough testing demonstrated less than 0.1 μCi ^{62}Zn/dose elution. The presence of ^{61}Cu radioisotopic contaminant was undetectable, assuring that the level of nonradioactive copper even in early elutions, was < 1 μg.

After overnight shipment, the generator was eluted to obtain doses for clinical study. Each eluted ^{62}Cu sample was measured after a 1–2 min delay in a Capintec, Inc. (Ramsey, NJ) dose calibrator to determine ^{62}Cu level before injection. Sterility tests, pyrogen tests, breakthrough and pH measurements were performed. Each injection was inspected for particulate content before injection. TLC was performed on each ^{62}Cu-PTSM dose before injection using ITLC strips and ethanol as a solvent. The strips were cut into three equal pieces and placed into separate tubes for counting in a gamma well counter. The ratio of counts in the top third to total counts in all pieces determined the radiochemical purity of the samples. The radiochemical purity ranged from 95.3% to 99%. The average injected dose was 17.96 mCi.

Patient Population

The study was approved by the Human Subjects Committee at the University of Wisconsin, and written informed consent was obtained from all volunteers before the PET study. Ten volunteers (5 women and 5 men; caucasian; age range 21–52 yr; mean = 32 yr) were recruited through newspaper advertisements (Table 1). After a brief medical history, the volunteers underwent a series of clinical tests including a physical exam, urinalysis, EKG and blood tests both before and after injection of ^{62}Cu-PTSM. Vital signs included blood pressure, temperature, pulse and respiration. Blood tests included hematology series of white blood cell count, hemo-

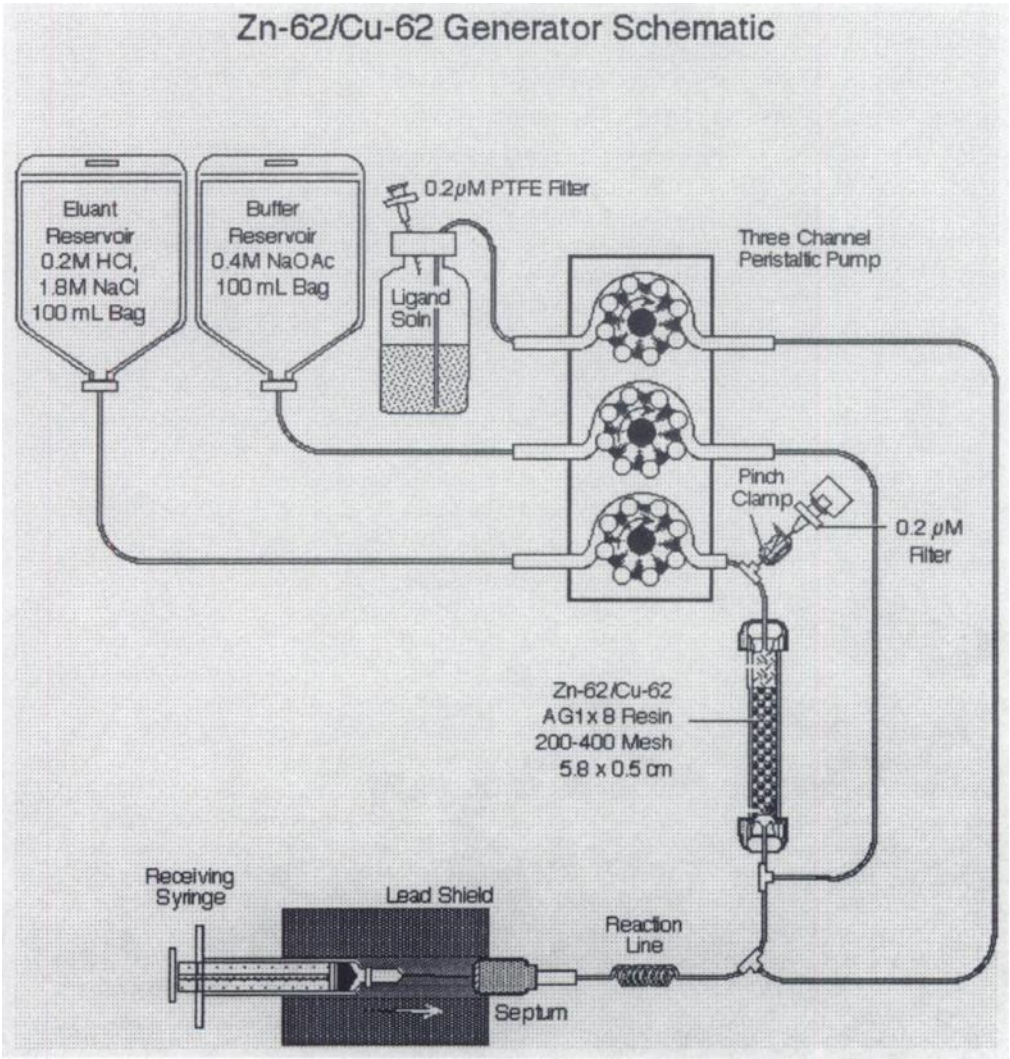

FIGURE 2. Schematic diagram illustrating plumbing of Proportional Technologies ^{62}Zn/^{62}Cu generator configured for on-line synthesis and delivery of ^{62}Cu-PTSM. Final ^{62}Cu-radiopharmaceutical was consistently delivered at >95% radiochemical purity into syringe at outlet of generator housing. Integrated steps of generator elution and in-line radiopharmaceutical synthesis require ~33 sec.

TABLE 1
Volunteer Subjects' Demographics

Subject no.	Sex	Age (yr)	Height cm (in.)	Weight kg (lb)	Injected activity (mCi)
1	F	43	160.0 (63)	59.1 (130)	18.87
2	F	52	157.5 (62)	61.4 (135)	16.95
3	M	31	170.2 (67)	63.6 (140)	15.49
4	M	30	190.5 (75)	81.8 (180)	11.91
5	F	21	172.7 (68)	125 (275)	20.6
6	F	21	167.6 (66)	61.4 (135)	14.44
7	F	22	171.4 (67.5)	54.5 (120)	19.72
8	M	33	167.6 (66)	65.9 (145)	18.77
9	M	27	177.8 (70)	80.4 (177)	17.45
10	M	39	188 (74)	93.2 (205)	25.41
Mean		32	172.3 (67.8)	74.6 (164)	17.96
Range		(21–52)	157.5–190.5 (62–75)	54.5–125 (120–275)	11.91–25.41

globin, hematocrit, platelet count and white blood count differential and blood chemistries of glucose, blood urea nitrogen, creatinine, Na^+, K^+, Cl^-, CO_2, calcium, phosphorous, uric acid, lactate dehydrogenase, aspartate transaminase, alkaline phosphatase, cholesterol and total protein. Urinalysis results included protein, glucose, ketone, Hemastix, bilirubin, specific gravity and pH and microscopic analysis for white blood cell, red blood cell, squamous epithelial cell and bacteria. Urine samples obtained after completion of the scanning procedure were counted immediately for 511 keV activity, and the volume was measured to calculate percent injected dose excreted in the urine. All female subjects had negative pregnancy tests before inclusion in the study.

PET Imaging Procedure

PET studies were performed at the University of Wisconsin PET Center on the GE Advance Scanner (General Electric, Inc., Waukesha, WI), 15.6 cm axial field of view, 35 slices, 3.8-mm in-plane resolution, whole-body tomographic scanner. For the PET studies, subjects were positioned in the supine position, feet first, in the scanner. Whole-body transmission scans were performed using three rotating ^{68}Ge pin-sources at six bed positions (5-min scan/position) starting from the top of the head and ending at the mid-thigh level. After the transmission scan, subjects received an intravenous bolus injection of ^{62}Cu-PTSM through a peripheral intravenously, and PET imaging was performed starting from the same position at the top of the head and repeating at the six positions down the length of the body to the mid-thigh level to acquire composite, continuous, whole-body resting PET scans. Three-minute PET static acquisitions were acquired at each of the six positions. Biodistribution data were obtained at three different time points by beginning the whole-body scans with the first slice starting at 6, 26 and 46 min after injection of ^{62}Cu-PTSM.

Image Analysis

Raw image data were reconstructed in transaxial format with attenuation correction using a 55-cm diameter field of view and a Hanning filter with a 8.5-mm cutoff. The attenuation-corrected image data were reformatted into 12 coronal slices (21.48 mm/slice) and used for ROI analysis. Using the whole-body attenuation correction scan, image emission count data were converted to mCi/cc. Each organ was then identified and a region of interest (ROI) was drawn inside the boundaries of the organ. The count densities in these regions in μCi/cc were then decay corrected to time of injection and divided by injected dose to give μCi/cc per mCi of injected ^{62}Cu-PTSM. These values were then multiplied by the standard organ weights and specific gravities given in International Committee on Radiation Protection publication on reference man (*20*) to obtain injected dose per organ. This assumes uniform tracer uptake in each organ.

Dosimetry Calculations

Resulting time-activity curves were extrapolated to time zero and then used to calculate radiation dose estimates. The residence times for each organ were calculated using the physical decay of ^{62}Cu (half-life 9.7 min) and the biological decay obtained from the fitted half-lives of the organ activities. The residence time was calculated as (*21*):

$$\text{Residence time (hr)} = \frac{A_h}{A_o}\left(\frac{1}{\lambda_{physical} + \lambda_{biological}}\right).$$

$$\frac{A_h}{A_o} = \text{fraction of dose in organ at } t = 0.$$

$$\lambda = \frac{\ln 2}{\text{half-life (hr)}}.$$

These values were then used in the Oak Ridge Associated Universities 1994 MIRD program, version 3.1 (*22*), to obtain a dosimetry table presented in both units of mGy/MBq and rad/mCi of individual organ dose and whole-body effective dose equivalent for a hermaphroditic adult phantom (*23*).

Statistical Analysis

Data on laboratory values are shown in Table 2. Values are expressed as the mean ± s.d. To further compare the pre- and postinjection values, paired Student's t-tests were performed and p values calculated. For biodistribution data, percent injected dose was determined for each organ as the mean ± s.e.m.

RESULTS

Pharmacology/Toxicology

Subjects pre- and postinjection physical examinations were without abnormalities. The mean value of all laboratory values, both pre- and postinjection, were within the normal range for our laboratory. No significant change in laboratory values occurred comparing preinjection with postinjection values. (Table 2, $p > 0.05$). Urinalysis results for all subjects were normal before and after injection, with the exception of one female subject who demonstrated elevated hemoglobin levels. This subject had a large amount of hemoglobin in the urine before injection, which decreased to moderate levels of hemoglobin postinjection. No subjects were excluded from the study on the basis of abnormal laboratory, electrocardiographic or physical examination findings.

Dosimetry/Biodistribution

A coronal, whole-body attenuation-corrected image in one subject with a 21.48-mm slice optimally transecting the heart is shown in Figure 3. Multiple whole-body image planes were used to draw ROIs in various organs for data analysis. Biodistribution results derived from these images in mean percent injected dose with error bars are shown in the form of time-activity graphs for each organ (Fig. 4). Because the percent injected dose per organ represents decay-corrected values, the resulting fitted exponential decay curves represent the biological half-lives of ^{62}Cu-PTSM in each organ. The biological half-lives of the organs are listed in Table 3 and demonstrate the slow washout rate from the various organs. Since previous articles have shown that virtually all of the ^{62}Cu-label is taken up by tissues in the first few cardiac transits (2 min) (*11,13,17*), residence times were calculated assuming instantaneous uptake of tracer.

TABLE 2
Laboratory Values*

Test	Preinjection	Postinjection	p value
Glucose (mg/dl)	89.7 ± 8.5	83.2 ± 6.1	0.97
BUN (mg/dl)	12.6 ± 2.0	11.8 ± 1.9	0.24
Creatinine (mg/dl)	0.9 ± 0.2	0.9 ± 0.2	22
Calcium (mg/dl)	8.9 ± 0.3	8.8 ± 0.3	11.22
Phosphate (mg/dl)	3.3 ± 0.3	3.3 ± 0.4	18.04
Uric acid (mg/dl)	4.9 ± 1.2	4.9 ± 1.1	14.08
LDH (U/liter)	145 ± 30	163 ± 46	5.50
AST (U/liter)	22.5 ± 7.1	25.4 ± 10.7	6.60
Alkaline phosphatase (U/liter)	77.4 ± 28.6	75.8 ±26.8	8.58
Cholesterol (mg/dl)	192.6 ± 44.2	194.8 ± 42.7	12.54
Total protein (g/dl)	6.7 ± 0.2	6.6 ± 0.3	7.26
Sodium (mmol/liter)	138.1 ± 1.2	138.9 ± 1.5	1.17
Potassium (mmol/liter)	3.9 ± 0.3	4.2 ± 0.3	1.54
Chloride (mmol/liter)	104.0 ± 1.3	104.2 ± 2.8	18.26
CO_2 (mmol/liter)	26.1 ± 1.7	26.0 ± 1.3	18.26
WBC (K/μl)	6.0 ± 1.3	6.4 ± 1.4	0.15
Hemoblobin (g/dl)	14.0 ± 1.5	14.0 ± 1.5	18.70
Neutrophil count (% total)	59.5 ± 8.4	57.9 ± 7.6	4.18
Lymphocyte count (% total)	28.7 ± 8.2	31.2 ± 7.5	0.66
Monocyte count (% total)	8.3 ± 3.2	7.5 ± 2.8	0.81
Eosinophil count (% total)	2.3 ± 1.4	2.3 ± 1.3	22
Basophil count (% total)	1.1 ± 0.3	1.0 ± 0.5	7.48

*Values are mean ± s.d.
BUN = blood urea nitrogen; LDH = lactate dehydrogenase; AST = aspartate transaminase; WBC = white blood cell.

Copper-62 uptake in the liver is shown in Figure 4. A positive slope of the time-activity curve for this organ suggests the accumulation of ^{62}Cu in the liver. No other organ demonstrates this positive slope of ^{62}Cu uptake over time. Attempts to identify tracer uptake in the gastrointestinal tract on image slices showed no significant uptake in the small or large bowel over time. The gallbladder was also not identified in any of the image slices. With the slow washout rate and the physical half-life of ^{62}Cu-PTSM (9.74 min), recovery of activity from the feces was not possible. Biliary excretion of ^{62}Cu does not appear to be significant in the absence of activity in the gallbladder or gastrointestinal tract. All 10 subjects showed only negligible traces of activity in the urine from samples obtained after the whole-body PET imaging procedure. Additionally, low levels of activity present in the gonads and bladder did not allow clear resolution of these organs and the surrounding tissue. The absence of significant bladder or urine ^{62}Cu activity and the negative slope of the time-activity curve for the kidney suggest insignificant urinary excretion of ^{62}Cu-PTSM.

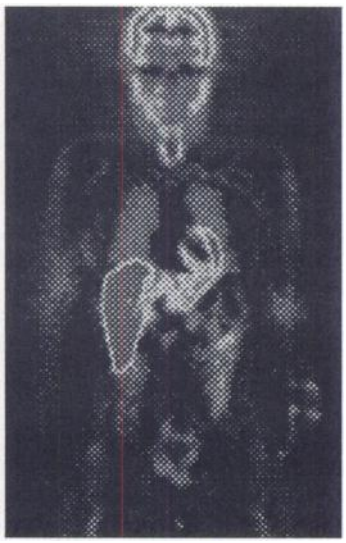

FIGURE 3. Whole-body image of one volunteer. Image is composite image of six bed positions reconstructed in coronal axis with 21-mm width through the heart. Seen on image is cardiac, hepatic, splenic, pulmonary, muscle, thyroid, cerebral and salivary gland uptake.

Dosimetry calculations used the Oak Ridge Associated Universities 1994 MIRD program, version 3.1 (*22*). The calculated residence times for each organ are shown in Table 3. These residence times were used to calculate absorbed doses for all target organs with the primary contributor to a target organ's total dose and the percent contribution to that organ's total dose (Table 4). The critical organ was the liver at 0.0887 rad/mCi, with slightly less exposure for the kidneys at 0.0805 rad/mCi. As expected, the exposure rates to the ovaries and testes were lower at 0.00911 and 0.00819 rad/mCi, respectively. The whole-body dose was 0.0111 rad/mCi.

DISCUSSION

This Phase I study demonstrates the safety and absence of toxicity of intravenously injected ^{62}Cu-PTSM. The basic procedure for preparation of ^{62}Cu-bis(thiosemicarbazone) complexes involves buffering the acidic $^{62}Cu^{2+}$/HCl generator eluate, followed by mixing with the bis(thiosemicarbazone) ligand. While previous work with ^{62}Cu-PTSM has used a fairly simple remote system for radiopharmaceutical synthesis (*11,16*), ^{62}Cu-radiopharmaceutical preparation has now been further simplified by integration of reagent mixing operations into the 20 × 30 × 300 cm housing of the modular Proportional Technologies generator unit. (Figs. 1 and 2).

The feasibility and ease of use of the ^{62}Zn/^{62}Cu generator system in clinical studies was apparent from this study. One potential disadvantage of the ^{62}Zn/^{62}Cu generator is the short half-life of the parent compound (^{62}Zn half-life = 9.13 hr) requiring generator replacement at 1–2 day intervals. However, this would allow centers to order the generator for days in which perfusion imaging is scheduled and performance of other studies on the remaining days of the week. This could substantially reduce costs for perfusion imaging compared with the currently available ^{82}Sr/^{82}Rb generator, which is shipped and purchased on a once per month schedule with an average cost of $30,000/month. Additionally, the ^{62}Zn/^{62}Cu generator system requires a more widely available, medium-energy cyclotron, as opposed to the high-energy cyclotron needed for ^{82}Sr production.

The time course of activity in organs such as the brain and heart, with biological half-times of 146 and 84 min, respectively, demonstrates the prolonged tissue retention in these organs. Some backdiffusion of tracer, as has been previously reported in the brain, may be occurring in several organs, accounting for some of the differences in biological half-lives (*17*). The shorter half-life in organs such as the lung ($T_{1/2}$ = 81 min), thyroid gland ($T_{1/2}$ = 39 min), and salivary gland ($T_{1/2}$ = 60 min), may be explained by varying degrees of backdiffusion of tracer in these organs. Additionally, differences in intracellular decomposition of the Cu-PTSM tracer resulting in ^{62}Cu entering normal copper cellular pools may explain some of the differences in retention times seen. Variations in the subcellular radiocopper distribution, after intravenous administration of Cu-PTSM, have been demonstrated in the murine brain and liver (*24*). The mitochondrial electron transport chain is the principal mechanism of Cu-PTSM reduction and retention in the murine brain (*25,26*). Reductive decomposition of Cu-PTSM by reaction with intracellular sulfhydryl groups is the proposed mechanism for retention in other tissues.

Dosimetry calculations identified the liver as the critical organ, receiving a dose of 0.0886 rad/mCi. This is in contradiction to previous estimates with ^{67}Cu-PTSM, where the

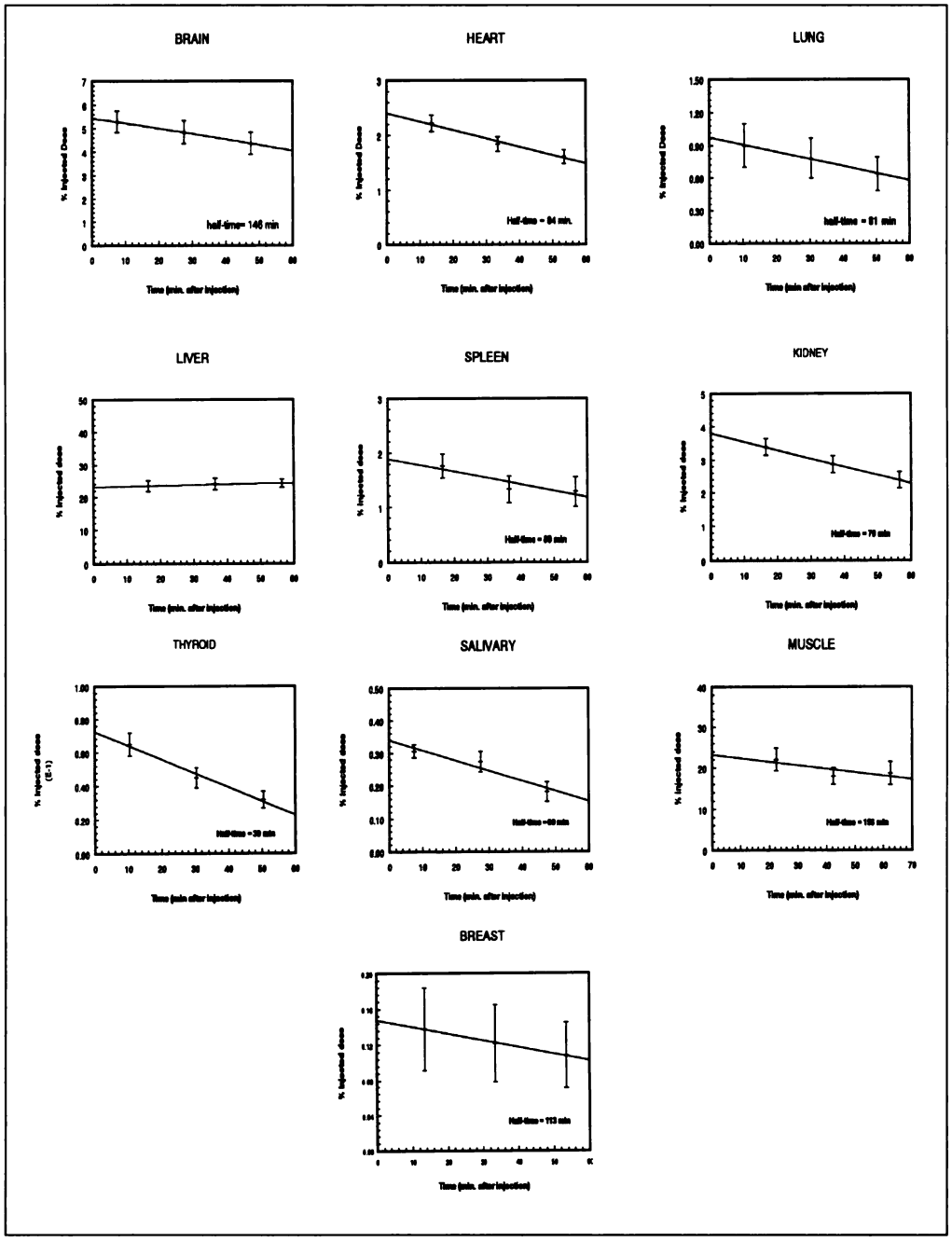

FIGURE 4. Slopes of time-activity curves for individual organs. Data from regions of interest drawn in various organs represent mean percent injected dose in a particular organ. Identical regions of interest drawn in each organ are shown plotted at three different time points (± s.e.m.). Because mean percent injected dose is decay corrected, resulting slope of line drawn through mean values represents biological half-lives of ^{62}Cu-PTSM in a particular organ.

kidney was suggested as the dose limiting organ (*6*). These previous estimates were based on biodistribution studies in the cynomolgus monkey and assumed in each organ the physical and biological half-lives were identical. Our study demonstrated a wide range of biological half-lives for various organs and the use of these biological half-lives should be expected to result in a more accurate account of dosimetry in various organs and the whole-body. Additionally, species-dependent albumin binding of Cu-PTSM, as demonstrated by Mathias et al. (*27*), might account for the different results reported in the cynomolgus monkey. The present results are in agreement with a previous article that the self-dose to the kidneys and liver is 0.0115 mGy/MBq and 0.0181 mGy/MBq, respectively, after ^{62}Cu-PTSM administration to humans (*28*).

The slope of the percent injected dose in the liver demonstrated a continued increase at 46 min after injection. This is in agreement with the study by Beanlands et al. in which the slope of the liver time-activity curve was also positive at 61 min (*13*). It has been demonstrated that, 1 min after injection of ^{62}Cu-62PTSM, none of the ^{62}Cu is in the form of Cu-PTSM. Copper-62-PTSM may combine with other substances in the bloodstream such as plasma albumin (*27*). This ^{62}Cu-albumin complex may deposit Cu(II) in the liver, where endogenous copper is incorporated into ceruloplasmin (*29*). Copper-62 trapped in the liver in this way might explain the positive slope of the percent injected dose for the liver and the absence of significant ^{62}Cu found in the gallbladder or bowel.

The biological half-life of ^{62}Cu in the kidney was 79 min, suggesting the kidney was not a major site for ^{62}Cu excretion. This is consistent with the low activity found in urine specimens

TABLE 3
Time-Activity Data of Mean Injected Dose

Organ	Percent at time				Biological half-life (min)	Residence time (hr)
	Point 0	Point 1	Point 2	Point 3		
Brain	5.49	5.29	4.84	4.37	146	0.012
Heart	2.47	2.22	1.84	1.61	84	0.005
Lung	0.99	0.9	0.72	0.64	82	0.002
Liver	23.22	23.46	24.05	24.23		0.054
Spleen	1.97	1.76	1.33	1.28	80	0.004
Kidney	3.93	3.4	2.86	2.38	79	0.008
Thyroid	1.46	0.07	0.05	0.03	39	0
Salivary	0.34	0.31	0.27	0.18	60	0.001
Muscle	23.66	22.1	18.07	18.75	156	0.052
Breast	0.15	0.14	0.12	0.11	113	0
Remainder of body	36.33	40.37	45.79	46.42	—	0.096

from subjects in this study; as the short half-life of ^{62}Cu results in its decay before it has a chance to accumulate significantly in the bladder.

The liver defines the maximum single injected dose at 56 mCi, using the limit of 5 rad to the critical organ per administration. At this injected level, the doses to the radiation sensitive organs are well below the 3 rad limit. The whole-body dose is 0.0111 rad/mCi, resulting in a 0.622 rad maximum single injection dose with a 56 mCi injection. These values actually represent upper-limit dosages since residence time calculations would have decreased with a wash-in factor that could not be accurately assessed. With the projected injection dose estimated to be in the range of 15 mCi per administration, use of serial injections for serial studies or clinical diagnosis should pose no problems for staying well below regulated dosage limits. The whole-body exposure compares favorably to other radiopharmaceuticals; the whole-body exposure for ^{99m}Tc-sestamibi is 0.4 rads/30 mCi or 0.013 rad/mCi (*30*). The effective dose equivalent for Cu-PTSM is also similar to other diagnostic studies; the effective dose equivalent for chest CT is 0.478 rads (*31*).

These human biodistribution results agree with previous studies, which have uniformly reported rapid uptake of ^{62}Cu-PTSM into the tissues in a nonspecific manner. All of the labeled tracer was taken up by the organs within the first few cardiac transits in general proportion to the cardiac output to the organ. The renal uptake is lower than expected, possibly due to the binding of Cu-PTSM to human serum albumin limiting its ability to be extracted at high rates of flow. Flow in the outer cortex of the kidney is quite high; thus, the lower-than-expected renal uptake is simply another manifestation of the physicochemical properties of Cu-PTSM in blood that disrupt the uptake-perfusion correlation at high rates of myocardial flow (*16*). The relative uptake in the heart and brain, when corrected

TABLE 4
Dosimetry Data

Target organ	Dose (mGy/MBq)	Dose (rad/mCi)	Primary contribution	%
Adrenals	3.09E-03	1.14E-02	Rem. body	67.4
Brain	7.24E-03	2.68E-02	Brain	97.6
Breasts	3.83E-04	1.42E-03	Rem. body	35.0
Gallbladder wall	3.54E-03	1.31E-02	Rem. body	59.4
LLI wall	2.40E-03	8.89E-03	Rem. body	90.4
Small intestine	2.59E-03	9.59E-03	Rem. body	85.4
Stomach	2.66E-03	9.86E-03	Rem. body	79.9
ULI wall	2.66E-03	9.83E-03	Rem. body	82.4
Heart wall	1.30E-02	4.82E-02	Heart wall	94.0
Kidneys	2.18E-02	8.05E-02	Kidneys	96.0
Liver	2.40E-02	8.87E-02	Liver	98.3
Lungs	2.25E-03	8.31E-03	Lungs	68.3
Muscle	1.96E-03	7.25E-03	Muscle	77.8
Ovaries	2.46E-03	9.11E-03	Rem. body	88.5
Pancreas	3.09E-03	1.14E-02	Rem. body	68.8
Red marrow	2.47E-03	9.16E-03	Rem. body	84.8
Bone surfaces	2.46E-03	9.12E-03	Rem. body	86.8
Skin	2.14E-03	7.94E-03	Rem. body	90.7
Spleen	1.78E-02	6.59E-02	Spleen	96.3
Testes	2.21E-03	8.19E-03	Rem. body	92.8
Thymus	2.41E-03	8.91E-03	Rem. body	84.9
Thyroid	4.92E-04	1.82E-03	Rem. body	49.7
Urinary bladder wall	2.38E-03	8.81E-03	Rem. body	90.4
Uterus	2.46E-03	9.12E-03	Rem. body	89.1
Total body	3.01E-03	1.11E-02	Rem. body	40.7
Effective dose	3.59E-03	1.33E-02	Liver	33.3

LLI = lower large intestine; ULI = upper lower intestine.

for the excess liver uptake, is related to the cardiac output to those organs. The fact that over 5% of the injected dose reaches the brain attests to the ability to cross the blood-brain barrier effectively. The high retention of ^{62}Cu-PTSM within organs is one of this radiopharmaceutical's advantages for PET imaging. Due to the slow washout rates and short physical half-life, it was not feasible to extend observations to the tail of the washout curve. The residence times demonstrated in Table 3 were calculated assuming instantaneous uptake combined with loss by physical decay and the biological washout defined by the fitted half-lives. With regard to a pharmacological effect of ^{62}Cu-PTSM, no consistent hemodynamic effect was seen, consistent with the low levels of ^{62}Cu-PTSM and H_2-PTSM, 4.3×10^{-3} μg and 2.1 μg, respectively, injected.

In calculation of organ distribution of tracer, we used published values of organ size and specific gravity. This approach was appropriate given the mean body mass of the volunteers. An alternative approach was reported recently by DeLoar et al. (*32*), in which organ volume was measured by separate, whole-body MRI. This approach may have particular application to populations differing in size from the 70-kg sample reported in the literature (*20*). The use of whole-body PET, then, offers the advantage of correction of attenuation and is particularly suited for the assessment of organ distribution of positron-emitting radionuclides. Whole-body PET imaging could still be used for ^{99m}Tc radiopharmaceuticals with the substitution of the positron emitter ^{94m}Tc for the ^{99m}Tc nuclide (*33*).

CONCLUSION

The results of this study demonstrate the safety and feasibility of ^{62}Cu-PTSM for clinical studies with PET. The favorable dosimetry will make it possible to perform several studies in the same patient. Furthermore, the availability of a compact generator system with a simplified synthesis method increases the ease of performing perfusion imaging with ^{62}Cu-PTSM. Further studies are in progress documenting the clinical efficacy of ^{62}Cu-PTSM for myocardial imaging compared to ^{99m}Tc-sestamibi.

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