Performance of a $^{62}Zn/^{62}Cu$ Generator in Clinical Trials of PET Perfusion Agent ^{62}Cu-PTSM

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The $^{62}Zn/^{62}Cu$ PET generator can be inexpensively produced and distributed from a single production site operating under typical good manufacturing practice guidelines. It therefore has the potential to greatly facilitate development of clinically practical PET. We report generator performance in a study in which ^{62}Cu-pyruvaldehyde-bis(n4-methylthiosemicarbazone (PTSM) myocardial perfusion imaging is compared with ^{99m}Tc-sestamibi in the diagnosis of coronary artery disease. The $^{62}Zn/^{62}Cu$ generator is an improved version of a previously reported system that employs automated synthesis of ^{62}Cu-PTSM. With this approach, the cumbersome step of ^{18}C purification has been eliminated. **Methods:** The ^{62}Zn (9.3 h half-life) parent isotope is prepared by proton bombardment of natural copper at 33 MeV. A typical target irradiated with 37.5 μA/h is delivered by 12:00 PM on the day it is to be processed. Purified ^{62}Zn obtained from the target is loaded onto the generator column in 2 mol/L HCl. The generator is eluted using an internal three-channel peristaltic pump, which delivers 2.25 mL eluant (1.8 mol/L NaCl, 0.2 mol/L HCl) through the generator column to elute the ^{62}Cu in 40 s. The same pump simultaneously pumps an equal volume of buffer (0.4 mol/L NaOAc) and 1 mL ligand solution (2 ppm PTSM, 2% EtOH) passing it through a septum into a 35-cc syringe preloaded with 28 mL sterile water. This solution is thoroughly mixed by agitation of the syringe and injected as a bolus through a 0.2 μm filter. The generator is eluted twice before shipping, providing quality assurance samples, and shipped to the clinical site by overnight delivery. Complete quality assurance testing is performed the evening before the generator reaches the clinical site. **Results:** A total of 34 generators have been produced and shipped to 2 clinical sites for a phase III Food and Drug Administration study. The load activity on the generators at 8:00 AM the day of clinical use was 1.7 ± 0.2 GBq (46.7 ± 5.6 mCi), and yield was 72% ± 16%. Breakthrough of ^{62}Zn was undetectable by high-purity germanium spectroscopy for all units. Radiochemical purity was 95.4% ± 2.4%. Volume delivered, pH, sterility, and bacterial endotoxin tests yielded passing results on all generators. The entire process of generator production, from target receipt to generator shipment, took less than 6 h and cost approximately $1000, including shipping charges and cyclotron cost. A total of 68 patients were injected with 2 ^{62}Cu-PTSM doses, with a mean injected activity of 0.8 ± 0.2 GBq (20.5 ± 5.3 mCi) with no adverse side effects. **Conclusion:** Results of this work confirm that the $^{62}Zn/^{62}Cu$ generator is an easily produced, transportable, and inexpensive source of PET radiopharmaceuticals, which can expand the field of clinical PET imaging by providing radiopharmaceuticals to sites not associated with cyclotrons.

Key Words: PET radiopharmaceuticals; $^{62}Zn/^{62}Cu$ generator; pyruvaldehyde-bis(n4-methylthiosemicarbazone); myocardial perfusion

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PET is a powerful imaging technique with many advantages over single photon imaging. However, the full potential of PET as a clinically useful diagnostic tool has not been realized, partly because of the lack of an economical and reliable source of broadly distributable PET radiopharmaceuticals. The expense of an in-hospital cyclotron and the associated staff required for its operation are simply too costly in today's managed-care environment. Many of the alternatives are equally unattractive. The $^{82}Sr/^{82}Rb$ generator system is very expensive, and the 76-s half-life of the daughter isotope significantly limits its versatility (*1,2*). The 68-min half-life of ^{68}Ga seriously limits the usefulness of the $^{68}Ge/^{68}Ga$ generator in a clinical setting by making multiple injection protocols very lengthy (*3,4*). Although FDG has proven to be clinically useful and is widely available, its 109-min half-life and cost of $550–$750 per patient dose restricts its role as well (*4–6*).

In contrast, the 9.74-min half-life of generator-produced ^{62}Cu is long enough for synthesis of chemically diverse radiopharmaceuticals (*7–9*), yet short enough for multiple repeated, same-day studies. Although the 9.3-h half-life of the parent isotope limits the shelf life of the $^{62}Zn/^{62}Cu$ generator to 1 d, the cost of production is low enough to make this generator an attractive candidate for continental distribution of PET radiopharmaceuticals (*10*). Unlike other reported $^{62}Zn/^{62}Cu$ generators, which rely on glycine or other organic eluant mixtures followed by ligand exchange reactions (*11,12*), this generator produces $^{62}Cu^{2+}$, which is chelated very strongly by pyruvaldehyde-bis(N^4-methylthiosemicarbazone) (PTSM) at very low ligand concentrations. Though similar in nature to a previously reported $^{62}Zn/^{62}Cu$ generator system that used a ^{18}C cartridge (*1,10,13*) to purify the final product, this fully automated generator avoids this unnecessary and time-consuming step to produce a >95% pure ^{62}Cu-PTSM injectable in less than 1 min. In addition, the processing of the irradiated copper target has been streamlined to minimize the time from end of bombardment (EOB) to generator loading to a fraction of that reported by

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many other investigators (*14,15*). Because PTSM is one of the most promising bis-thiosemicarbazone agents previously investigated for myocardial imaging (*16–20*), we investigated the performance of our generator for production of this agent in the clinical PET setting. We report generator performance in a study in which $^{62}Zn/^{62}Cu$ generators were prepared and shipped to clinical sites for evaluation of ^{62}Cu-PTSM PET imaging compared with ^{99m}Tc-sestamibi in the diagnosis of coronary artery disease.

MATERIALS AND METHODS

Production of ^{62}Zn was accomplished by proton irradiation of natural copper at the Positron Diagnostic and Research Center, University of Texas Health Science Center, Houston, TX, using the $^{63}Cu(p,2n)$ and $^{65}Cu(p,4n)$ reactions. A production energy of 33 MeV and a target thickness of 1.62 mm optimized ^{62}Zn yield, and minimized production of the unwanted byproducts, ^{61}Cu, ^{64}Cu, ^{63}Zn, ^{65}Zn, ^{58}Co, and ^{57}Ni. The target material used was 99.99% pure A102 oxygen-free high-conductivity copper (Farmers Copper, Galveston, TX). After a brief cool-down period to allow the short-lived contaminants to decay, a typical target irradiated with 37.5 μA/h was delivered and immediately processed for overnight delivery of the generator. EOB ^{62}Zn yields were typically 0.33 GBq/μA/h (9 mCi/μA/h) using a standard 45-min target irradiation.

To minimize radiation exposure during the processing of the target and loading of the generator, the process hot cell was lined on all sides with 5 cm lead. The top of the central cell was covered with a 2.5-cm lead shield containing a 5.5-cm hole facilitating fume collection and remote viewing. The central cell, together with shielding, was placed inside a sealed acrylic box inside a fume hood. The fumes produced by the boiling acid inside the cell were collected and pumped through a scrubber filled with a solution of KOH, through 2 aerosol traps, and finally exhausted into the fume hood. The separation column, the generator column, the final product tube, the waste container, and the loading syringe on top of the generator module were all contained within lead pigs that provided more than 5 cm of shielding on all sides. Using solenoid valves and peristaltic pumps, the entire process was remotely controlled from a distance of more than 15 feet, where the radiation level was below 0.05 mR/h. Monitoring was accomplished using mirrors, a telescope, and strategically placed miniature Geiger probes.

The separation of ^{62}Zn from the target copper was accomplished in a brief procedure using anion exchange column chromatography as previously described by Robinson et al. (*21*). The target was transferred to a Teflon beaker inside the hot cell and dissolved in 10 mL hot 70% HNO_3. The resulting $Cu(NO_3)_2$ was converted to the chloride form by two 10-mL and one 5-mL additions of 12 mol/L HCl, followed by boiling until precipitate formation at each step. After the third addition, the solution was evaporated to complete dryness to ensure removal of NO_3^-. This precipitate was then reconstituted in 2 mol/L HCl and, after cooling, loaded onto a 0.75 × 4.2-cm AG1X8 anion exchange resin (Bio-Rad, Richmond, CA) column. In 2 mol/L HCl an anionic complex of Zn is formed. Cu, Co, Ni, and Fe are very weakly complexed, so that the ^{62}Zn is strongly bound by the resin, whereas the transition metal contaminants are freely washed from it (*21,22*). After loading, the column was washed with 20 column volumes (36 mL) of 2 mol/L HCl to ensure complete elimination of contaminants. The ^{62}Zn was then eluted from the column with 8 mL sterile water for injection ([SWFI] Baxter Healthcare Corp., Deerfield, IL) into a Teflon container to which 1.6 mL 12 mol/L HCl was added to bring the solution to 2 mol/L concentration. After thorough mixing, the solution was loaded onto the generator column, followed by a 4 mL 2 mol/L HCl wash.

The modular generator unit contains a 3-channel internal peristaltic pump; a 0.75-mL, lead-shielded, glass column loaded with AG1X8 anion exchange resin; a tubing set; and 3 sterile nonpyrogenic partial additive bag (PAB) mixing containers (B. Braun/McGaw Medical, Inc., Irvine, CA). The 3 solutions on board the generator are contained in the mixing containers and are: eluant (1.8 mol/L NaCl, 0.2 mol/L HCl), buffer (0.4 mol/L NaOAc), and ligand solution (2 ppm PTSM in 2% EtOH). The tubing set, column, 0.2-μm loading filters, and all connections were assembled, filled with sterile 0.03 mol/L HCl, and autoclaved as a single unit (Fig. 1). The PAB mixing containers and sterile output septum were added afterward in a laminar flow hood using sterile technique (Fig. 2). The generator was eluted by pressing a button and activating the internal pump for 40 s. In a 40-s elution, the peristaltic pump delivers 2.25 mL eluant through the column, while simultaneously delivering an equal volume of buffer, which mixes with the eluant immediately on emerging from the generator column. By incorporating a smaller tubing size, the same internal pump simultaneously delivers 1 mL ligand solution, which is combined with the buffered eluant. The resulting mixture is then passed through a reaction line to allow 2.3 s for full reaction before emerging from the output septum. The output septum is mounted in the lid of the generator module, and the elution is automatically delivered into the collection syringe (Fig. 3). The generator lid is also equipped with an ample radiation shield, providing 5 cm of lead thickness in all directions. The collection syringe is previously loaded with 28 mL SWFI to correct the isotonicity of the injectable.

Each generator was eluted for quality control at 15 and 60 min postloading time and then shipped to the clinical site by overnight delivery. After the generator was shipped, the 2 test elutions were subjected to a battery of quality assurance tests. Elution volume was measured to within ±0.1 mL, and pH was determined using narrow range (3.6–6.1) pH indicator sticks (J.T. Baker, Inc., Phillipsburg, NJ). Shortly after each elution, ^{62}Cu radioactivity was measured using a CRC-15R (Capintec, Ramsey, NJ) with a calibration setting of 448. Generator yield was determined by dividing the ^{62}Cu activity in the elution by the decay-corrected ^{62}Zn activity on the column. The radionuclidic identity of ^{62}Cu was established by the presence of peaks at 511, 875, and 1173 keV (196%, 0.147%, and 0.335% abundance, respectively), using a Canberra model GR0820 HPGe detector (Canberra, Meriden, CT). The level of potential radionuclidic contaminates, including ^{61}Cu (3.4 h), ^{64}Cu (12.7 h), ^{63}Zn (38.1 min), ^{58}Co (71 d), ^{65}Zn (244 d), ^{57}Ni (36 h), and ^{62}Zn breakthrough (9.26 h) were evaluated by collecting a 1000-s spectrum with the elution syringe placed directly on the surface of an HPGe crystal. The spectrum was collected 3 h after elution, ensuring the total decay of ^{62}Cu. The absence of ^{61}Cu γ-radiation (656 keV) in the spectrum was used to place an upper limit on the presence of cold copper contamination in the injectable, based on the known production rate of ^{61}Cu decay corrected to the measurement time. Radiochemical purity of ^{62}Cu-PTSM was determined by instant thin-layer chromatography (ITLC). A volume of 0.5 μL of each elution was spotted onto a 6.5-cm strip of ITLC-SG chromatography paper (Gelman Sciences, Ann Arbor, MI). This strip was then dried for 1 min and developed with absolute EtOH (AAPER; Alcohol and Chemical Co., Shelby-

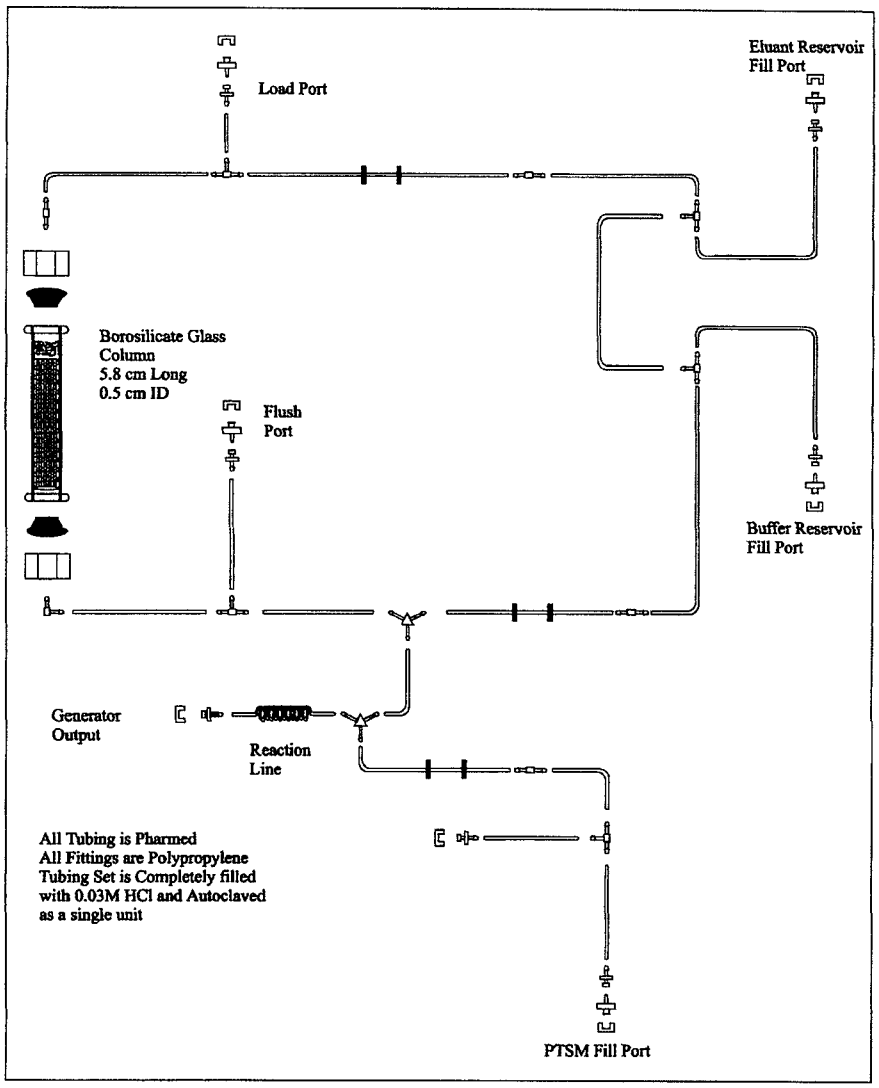

FIGURE 1. $^{62}Zn/^{62}Cu$ generator tubing set assembled for autoclaving.

ville, KY). The strip was then cut into thirds, counted in a Searle 1197 well counter, and decay-corrected to determine the percentage of activity that traveled with the solvent front.

Sterility was evaluated by adding 1 mL elution to a 21-mL vial of trypticase soy broth (TSB). A second 1-mL sample was added to a 21-mL vial of fluid thioglycollate medium (FTM). These were then incubated for 14 d at 24° and 34°C, respectively (BBL, Cockeysville, MD). Samples from each generator were pH adjusted to 7.0 by dropwise addition of 0.1 mol/L NaOH standard (Mallinckrodt, Phillipsburg, NJ) so that bacterial endotoxin testing (BET) could be performed by limulus lysate assay. Negative, positive, and positive product controls were used for each test (Associates of Cape Cod, Woods Hole, MA). With the exception of the sterility tests, all of the quality assurance tests were completed before the generator reached the clinical site.

At the clinical site, the generator was again tested for pH, elution volume, delivered dose, ^{62}Zn breakthrough, and radiochemical purity. Before administration, each dose was thoroughly mixed by agitation and measured for activity. Injection was performed as a slow bolus of 20–30-s duration, followed immediately by rapid saline drip. Imaging began 2 min after injection. Patient radiation dose was estimated using the Oak Ridge Associated Universities 1994 MIRD program version 3.1 (MIRDOSE3; Oak Ridge Associated Universities, Oak Ridge, TN), using biodistribution measurements obtained by whole-body PET scanning, as previously described by Wallhaus et al. (*23*). After clinical use, the spent generator was returned, together with the last elution collected at the site. This final elution was also tested for pH, sterility, pyrogenicity, and radionuclide contaminants as described earlier.

After return from the clinical site, the generator column was washed twice with 20-mL aliquots of SWFI to remove the low levels (~13.9 MBq [~375 mCi]) of long-lived ^{65}Zn and any remaining ^{62}Zn. Using sterile technique, the eluant, buffer, and ligand reservoirs were refilled, and the loading filter replaced, preparing the generator module for reloading. Each generator module was recycled for 1 mo, after which the resin was replaced, the tubing set autoclaved, and the module outfitted with new bags of sterile solution, filters, and septa. This recycling process substantially reduces labor, and therefore ultimately the cost of the radiopharmaceutical, without compromising patient safety.

RESULTS

A total of 34 modular $^{62}Zn/^{62}Cu$ generators have been produced and shipped to 2 clinical sites for use in a phase III

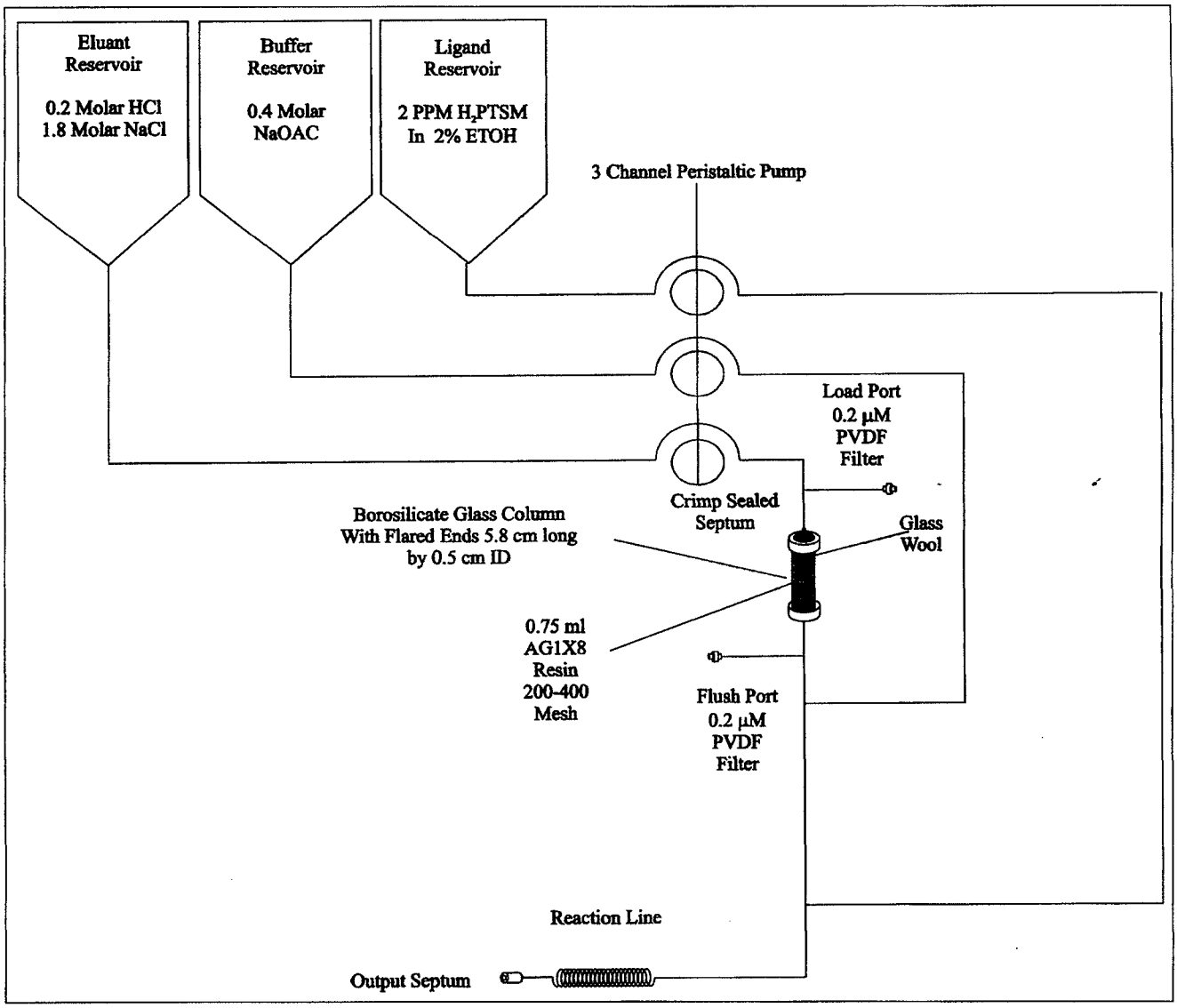

FIGURE 2. $^{62}Zn/^{62}Cu$ generator schematic.

Food and Drug Administration (FDA) study (Investigational New Drug 49462), 24 to the University of Texas Health Science Center and 10 to the University of Wisconsin Medical School. The load activity on the generators at 8:00 AM the day of delivery to the clinical site was 1.7 ± 0.2 GBq (46.7 ± 5.6 mCi), and the elution yield of ^{62}Cu was 72% ± 16%. Breakthrough of ^{62}Zn, as well as other radiocontaminants, was undetectable by HPGe spectroscopy on all units. Because ^{61}Cu was never detected in any of the generator elutions, an upper limit level of cold copper in the injectable was established at less than 0.01 µg per dose (the lower limit of detection by HPGe spectroscopy). Volume delivered was 5.5 ± 0.2 mL for 40-s elutions, and pH was consistently between 4.7 and 5.0. The mean radiochemical purity of ^{62}Cu-PTSM, as determined by ITLC, was 95.4% ± 2.4%. Every generator passed sterility and BET tests on a sample elution collected and tested before reaching the clinical site. (The sterility test incubation period was started the day the generator was manufactured, but required 14 d.) The eluate also always remained sterile and pyrogen free in the final elution, collected at the clinical site, and returned for testing. A total of 68 patients were injected with 2 doses each, the first at rest and a second after dipyridamole-induced stress, with a mean injected activity of 0.8 ± 0.2 GBq (20.5 ± 5.3 mCi). For both injections combined, the average patient whole-body radiation dose was 0.43 ± 0.4 rads; the liver (critical organ) dose was 3.42 ± 0.32 rads. No adverse side effects were reported in any of these patients. A representative patient scan is shown in Figure 4, with rest study (left) and dipyradimole study (right).

The entire production process, from receiving the target to shipping the generators, took <6 h. Personnel radiation exposure for an entire production, including quality assurance, was typically <6 mR whole-body dose for a normal 12.2-GBq (330-mCi) target. The cost of the $^{62}Zn/^{62}Cu$ generators produced in the study was approximately $1000

FIGURE 3. Clinical $^{62}Zn/^{62}Cu$ generator with collection syringe ready for insertion.

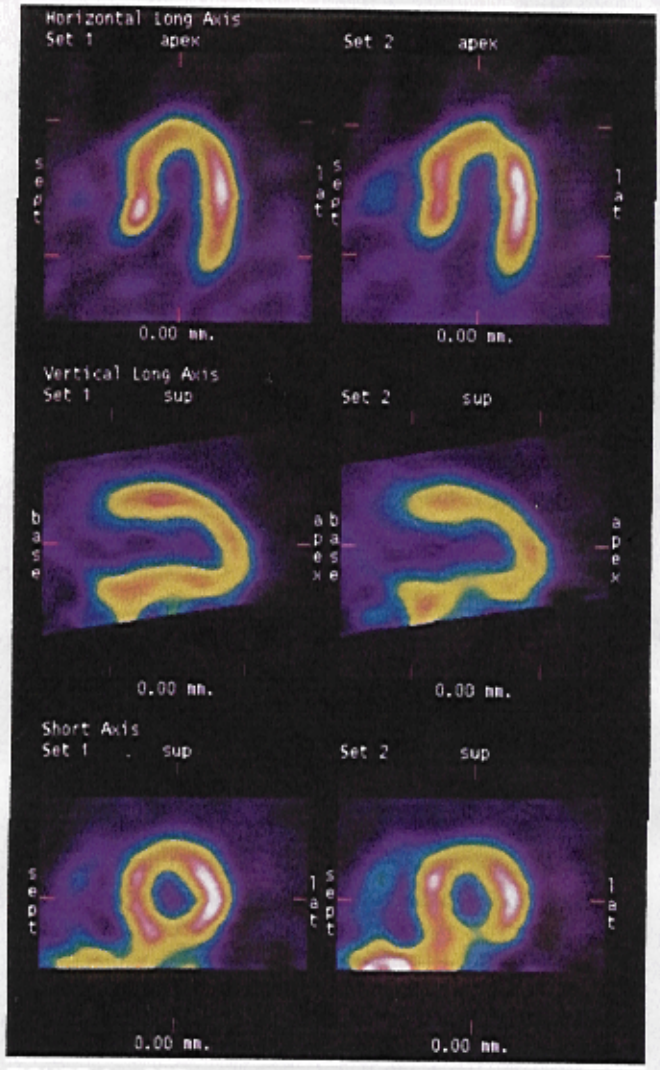

FIGURE 4. PET scans show small reversible ischemic defect in posterior wall.

each, including shipping charges, with the majority of the expense attributable to target irradiation cost.

DISCUSSION

The results of this endeavor confirm that the $^{62}Zn/^{62}Cu$ generator is an easily produced, transportable, inexpensive, and reliable source of PET radiopharmaceuticals. The 9.74-min half-life of ^{62}Cu makes it ideal for repeat studies, as well as combination studies with other radiopharmaceuticals such as FDG. With next-day air delivery, the modular generator can be shipped anywhere in the continental United States from a single GMP-controlled processing facility. The advantages are (a) that a single processing facility can economically conform to FDA regulations, and (b) that PET radiopharmaceuticals can be made available to widely distributed sites not associated with cyclotrons.

The diverse coordination chemistry of copper may make ^{62}Cu one of the more adaptable β^+ emitters in the pharmacopoeia. The innovative design of this modular $^{62}Zn/^{62}Cu$ generator, providing in-line synthesis of ^{62}Cu radiopharmaceuticals, may be adapted to a wide variety of other ligands, including ethylgloyoxal bis(thio-semicarbazone) (ETS), *n*-propylglyoxal bis(thiosemicarbazone) (*n*-PrTS), diacetyl-bis(N^4-methylthiosemicarbazone) (ASTM), and human serum albumin dithiosemicarbazone (HSA-DTS), as well as several other copper ligands that have the potential to become tissue- or regional-specific imaging agents with broad applications. The first 4 of these—^{62}Cu-ETS, ^{62}Cu-*n*-PrTS, ^{62}Cu-ASTM, and ^{62}Cu-HSA-DTS—can be readily produced with the reported generator.

Many investigators have looked at generator-produced ^{62}Cu-PTSM for myocardial and cerebral imaging over the past few years, but few if any have considered the cost of producing this radiopharmaceutical. Although cost was not the only focus of this investigation, it was a major consideration as was clinical performance during actual use. The biggest criticism of the $^{62}Zn/^{62}Cu$ generator has been that the short half-life (9.3 h) of the parent isotope limits the generator's usefulness to a single day. However, with an anticipated production cost of less than $500 per unit, the generator's capability to produce a clinically useful dose

every 30 min for a full day is very attractive. By eliminating the expense of an in-hospital cyclotron and the associated personnel, the cost of PET imaging can become competitive with tracers such as ^{99m}Tc-sestamibi and provide superior diagnostic quality, including improved resolution and quantitative attenuation correction. The ability of a clinical site to order a generator for only the days it is needed also offers a significant advantage over the ^{82}Sr/^{82}Rb generator, which must be procured for a monthly cycle. Finally the automated operation of the ^{62}Zn/^{62}Cu generator, together with its compact size, is compatible with easy, daily recycling. Because of these combined features, this generator offers a potential new horizon in the distribution of PET radiopharmaceuticals.

CONCLUSION

A new, fully automated ^{62}Zn/^{62}Cu generator system has been shown to be a reliable and low-cost source of PET radiopharmaceuticals that can be conveniently used for myocardial perfusion imaging in a clinical setting.

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