Development and Clinical Performance of an Automated, Portable Tungsten-178/Tantalum-178 Generator

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An automated, portable $^{178}W/^{178}Ta$ generator system has been developed for use in first-pass radionuclide angiography studies with the multiwire gamma camera. Eluant (0.03N HCl, 0.1% H_2O_2) and buffer (0.13 N Na_2HPO_4) are delivered with a dual channel peristaltic pump. The generator column is a borosilicate glass tube with 30 μm fused glass frit containing 0.75 ml AG1X8 anion exchange resin. This column and associated plumbing are assembled, integrally autoclaved, and then connected to sterile eluant and buffer containers. Automatic push-button elution directly into an injection syringe is provided. Three such generators have been employed in the study of 78 patients in the catheterization laboratory utilizing a mobile, multiwire gamma camera. Over a 3-mo period, 301 sterile pyrogen-free doses ranging from 15 to 99.5 mCi were supplied with a mean breakthrough level of 2.1 ± 3.6 μCi. This automated, portable, high-yield $^{178}W/^{178}Ta$ generator represents a major advancement that will significantly facilitate first-pass radionuclide angiography with ^{178}Ta and the multiwire gamma camera.

J Nucl Med 1991; 32:2158–2161

The radionuclide ^{178}Ta has highly advantageous properties for use in nuclear medicine as a result of its short, but not too short, half-life of 9.3 min. Other currently used cardiac agents (^{99m}Tc and ^{201}Tl) have half-lives of 6 hr or more and impose many clinical limitations both as a result of high-radiation dose levels and the absence of physical decay during an acceptably brief clinical visit. Radiation dose levels restrict the maximal injectable dose of these agents to about 30 mCi and 3 mCi, respectively, while long physical decay time makes it difficult to perform important multiple serial studies. The short 9.3 min half-life of ^{178}Ta provides a reduction of patient dose relative to ^{99m}Tc by a factor of 20 and relative to ^{201}Tl by a factor of 200 and a commensurate increase in injectable level (*1*). These very high injectable levels make the agent very effective for first-pass radionuclide angiography (FPRA) studies, particularly when used with the high-speed multiwire gamma camera. The advantages of ^{178}Ta over other experimental short-lived agents for FPRA applications, most notably gold-195m and iridium-191m, are significant and have been previously discussed (*1*).

Although applications of ^{178}Ta have been limited to the FPRA area at present, the synthesis of potential myocardial perfusion agents has recently been shown to be practical (*2*). The 9.3-min half-life of ^{178}Ta offers many advantages for this and other tissue specific imaging applications. As in the FPRA application, very high injectable doses of such agents would be feasible, shortening imaging times and improving image quality, particularly in tomographic imaging. The short half-life also provides the benefit of allowing very important multiple procedures such as rest/stress perfusion imaging within an acceptably short, single clinical visit.

For clinical use, ^{178}Ta is delivered from a generator based on the 21.7-day parent wolfram-178, which is readily and economically produced by cyclotron irradiation (*3,4*). This generator has a long shelf-life of 30 days and can support hundreds of studies during this period. Optimal imaging of ^{178}Ta is limited to the new multiwire gamma camera, which is capable of providing superior imaging and count rate characteristics at the relatively low energy (60 keV) of the agent and is highly insensitive to its low abundance, high energy gamma emissions (*5–8*). One of the important recent advances of this camera is its mobility, providing convenient application at the bedside. This portability, combined with the need to elute the $^{178}W/^{178}Ta$ generator for each patient study at a nearby location, produces unique requirements for the generator. In particular, convenience of use is a very important factor and portability of the generator, if not essential, is highly desirable.

A clinical $^{178}W/^{178}Ta$ generator has been previously reported (*1*). This system utilized a manual elution mechanism, providing uptake of an eluant volume from a reservoir and delivery through the generator by manual syringe action. Although this system has been successfully and extensively employed by us, it has several drawbacks (*5,6*). First, it is subject to human error both in eluant volume delivered and in the pressure of such delivery.

Received Dec. 28, 1990; revision accepted May 28, 1991.

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Second, such a syringe delivery system in use over several weeks of operation can potentially compromise sterility. Third, this system does not provide pH adjustment, requiring that buffer solution be preloaded into the receiving syringe, which is a significant inconvenience.

These undesirable features have been eliminated and convenience has been improved through a new design that incorporates a dual-channel peristaltic pump providing simultaneous delivery of eluant and buffer solution. In addition to automatic dose delivery, this system has removable pump tubing sections allowing preassembly of all plumbing into a single, sealed, autoclavable unit. After autoclaving, this unit is integrally installed into the generator without compromise of sterility and provides a completely sealed system throughout the extended use period of the generator, minimizing the possibility of pathogen contamination. The system, furthermore, is highly-automated, requiring only insertion of a syringe into an output port and the push of a button to initiate isotope delivery. We report development and early clinical performance of this generator.

MATERIALS AND METHODS

Apparatus

Column and Plumbing Design. The generator operational schematic is shown in Figure 1. Eluant and buffer are drawn from sterile reservoirs and delivered, respectively, to the generator column and to a "Y" connector at the column output. A dual-channel peristaltic pump performs this function utilizing autoclavable silicone tubing. Tubing inside diameter (i.d.) sizes of 1.30 mm and 0.64 mm provide a flow ratio of 3/1 yielding the required mix ratio of eluant to buffer, respectively, and an eluant delivery rate of 4 ml per min.

The generator column is constructed from 8 mm outside diameter (o.d.), 5 mm i.d. borosilicate glass tubing with ends flared into standard 11-mm vial closures, and a fused 30-μm glass frit near one end. The column is prepared by filling the tube above the glass frit with 0.75 ml of AG1X8, 200–400 mesh anion exchange resin in chloride form (Bio-Rad, Richmond, CA). A glass wool plug of 11-mm length is inserted over this resin bed and the ends capped with ethylene-propylene-diene (EPDM) 11-mm vial closures.

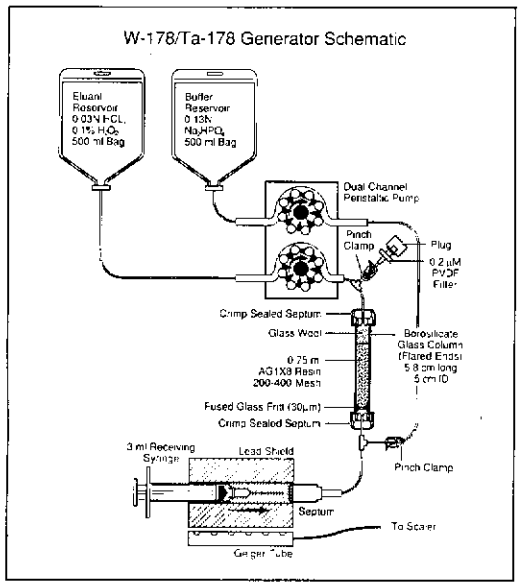

FIGURE 1. Tungsten-178/Tantalum-178 generator schematic.

The column is enclosed in a lead shield of contoured shape, providing a minimum of 5 cm of shielding in all directions. With 200 mCi ^{178}W loaded on the column, this shielding provides a dose at the surface of the exterior generator housing ranging from 1 mR/hr to 10 mR/hr. The maximum dose rate at one foot from the surface is 2 mR/hr. Entry into the column is provided by insertion of polypropylene "I" connectors through the prepunctured septa. Entry into the eluant and buffer reservoirs is achieved similarly through septa built into these containers. The eluant and buffer are mixed at the output of the generator column and the mixture is then delivered through a silicone tube to a barb-to-female luer bulkhead fitting to which is installed an intermittent injection port. This port is oriented in a vertical direction and surrounded by a 7.5-cm diameter by 8-cm long, cylindrical, lead shield provided with a vertical 1-cm channel. A loading port is provided near the input to the generator column. Loading is performed through a 13-mm Acro LC13 0.2 μm filter (Gelman Sciences, Ann Arbor, MI).

Automated Volume Delivery. The volume delivered by the peristaltic pump is monitored by electronically counting the number of rollers passing over the pump tubing. Pump action is begun by depressing a push button and continued until the count appropriate for the desired volume is reached.

We have previously demonstrated that cooling of the ^{178}W/^{178}Ta generator to 4°C provides a substantially increased yield. (*1*). This cooling is provided by incorporation of the entire generator into a compact refrigeration unit. In addition to cooling, this unit provides a convenient, sturdy, sealed enclosure (see Fig. 3).

Chemical Preparation

Sterile eluant (0.03N HCl, 0.1% H_2O_2) is prepared by the following procedure. A volume of 500 ml of solution is made up in a pyrogen-free volumetric flask, using 1.25 ml of concentrated HCl, 17 ml of 3% H_2O_2 (USP), and sterile water for injection (SWFI) to make 500 ml. Within a laminar flow clean bench, this solution is dispensed into an empty, sterile, pyrogen-free, 500 ml plastic bag, utilizing a sterile transfer set (Baxa Corporation, Englewood, CO) connected to an Exacta-Med pharmacy pump (Baxa) through a 0.22 μm, 37 mm filter assembly (Baxa). The H_2O_2 content is confirmed by titration with 0.1N $KMnO_4$ solution in 1N H_2SO_4 and the HCl content by titration with 0.1N NaOH to a phenolphthalein endpoint. (*9*)

Sterile buffer solution (0.13N Na_2HPO_4) is prepared by an analogous procedure utilizing 17.4 g of dibasic sodium phosphate heptahydrate, 9.7 g of sodium chloride (USP) and SWFI to make 500 ml. Sterile transfer to 500 ml plastic bags is carried out as above. This solution, when mixed with eluate 1/3, produces an isotonic pH 6.2–7.0 solution. The concentration of Na_2HPO_4 in the buffer is confirmed by titration with 0.1N HCl to a methyl orange endpoint (*10*).

Assembly and Loading

The entire plumbing assembly is filled with eluant and prepared for autoclaving as shown in Figure 2. Autoclaving is

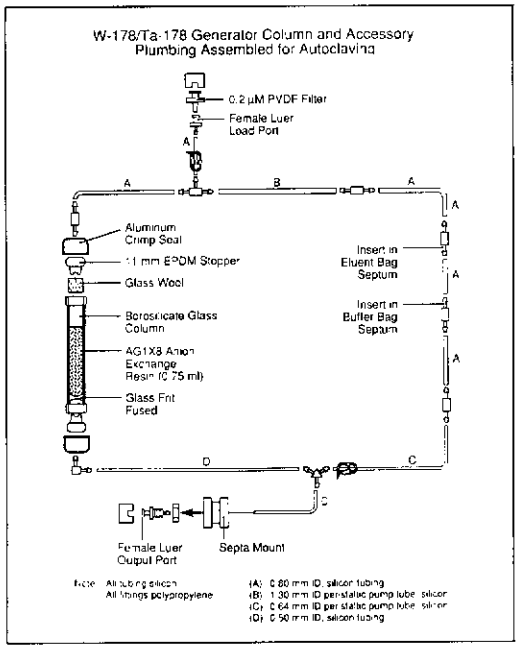

FIGURE 2. Tungsten-178/Tantalum-178 generator column and accessory plumbing assembled for autoclaving.

performed at 120°C for 20 min. The generator is prepared for loading by installing the generator column in the lead pig, the peristaltic pump tubes in the peristaltic pump, and inserting the polypropylene "I" fittings of eluant and buffer lines through the septa of their respective reservoirs. Loading is performed by pumping 2 ml of ^{178}W in 0.1N HCl, 1% H_2O_2, 0.02N HF solution into the loading port at a rate of 0.1–0.2 ml/min. Then the column is washed immediately with 40 ml of eluant. Immediately following this wash, an additional 1 ml is eluted to provide solution for limulus lysate pyrogen analysis and bacterial cultures. After 45 min, a standard 1.2 ml elution is performed. This elution is assayed immediately and decay corrected to the beginning of the elution. The generator yield is calculated as the percentage of decay corrected ^{178}Ta activity to the ^{178}W loaded on the column (the theoretical maximum ^{178}Ta activity). After a minimum 3-hr delay, this elution is again assayed for ^{178}W and the breakthrough of the generator calculated as the ratio of this activity to the loaded ^{178}W.

Operation of the System

To elute the generator, the output port lead shield (Fig. 3) is removed and the injection site wiped with a sterile alcohol swab. After shield replacement, a sterile 3-ml syringe with a 25-gauge needle is inserted through the shield penetrating the septum. The delivery button is then pressed and the built-in dual channel peristaltic pump automatically delivers a 1.2 ml dose of ^{178}Ta in buffered isotonic solution ready for injection. Dose assay is provided by counting with the built-in Geiger detector for 6 sec beginning immediately at the end of elution. Complete elution and assay is provided in 21 sec.

Clinical Generators

Three generators of the described design were used to study cardiac function in 78 patients undergoing percutaneous transluminal coronary angioplasty (PTCA). This study was carried out under an FDA-approved IND and informed consent was obtained from all patients. Both the portable generator and the multiwire gamma camera were operated in the catheterization laboratory to acquire high count-rate FPRA studies at baseline and during coronary balloon inflation, thereby documenting the effect of transient (~45 sec) coronary occlusion at various coronary sites. The practical implementation of this protocol was very demanding. The FPRA study during coronary occlusion was performed over the last 30 sec of 1-min balloon inflation. For this study, the fluoroscopy camera was raised, the multiwire gamma camera quickly positioned over the patient's chest, the $^{178}W/^{178}Ta$ generator eluted, the angioplasty balloon inflated, and first-pass ^{178}Ta injection performed 30 sec into the inflation. It was very important to minimize the interruption of the angioplasty procedure during which no fluoroscopy was available, which included the time to elute and inject the ^{178}Ta. Thus, rapid and convenient elution of the generator was of great importance.

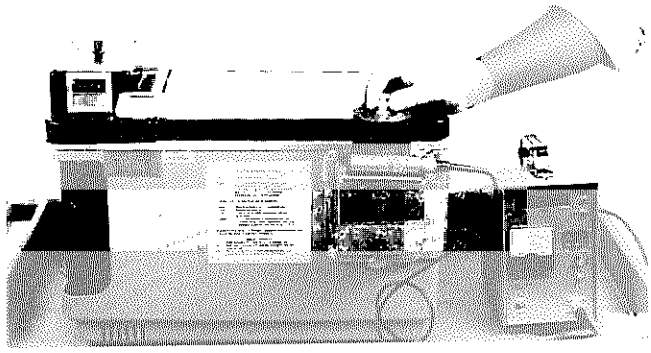

FIGURE 3. Clinical $^{178}W/^{178}Ta$ generator.

The three generators used in this study were also used for routine diagnostic FPRA in the nuclear cardiology laboratory over the 3-mo period of these studies. The generators were loaded with 152, 222, and 235 mCi of ^{178}W. To document breakthrough performance, on each day of clinical use each generator was eluted early in the morning and late in the afternoon. Those samples were retained and measured at least 3 hr after elution to obtain the generator breakthrough level. Each generator used in this study was examined for pyrogens and sterility prior to clinical use and at the end of the 30-day clinical use period.

RESULTS

The three clinical generators were eluted 113, 96, and 200 times and had an average ^{178}W breakthrough of 2.5 ± 2.5 µCi, 3.4 ± 2.8 µCi, and 1.2 ± 0.5 µCi. The delivered dose of ^{178}Ta ranged from 15–99.5 mCi. Sterility and pyrogen tests were negative, both for initial samples and those taken after 30 days of use.

Figure 4 shows the yield and breakthrough performance of the largest of these generators (235 mCi ^{178}W). The unit was eluted 125 times for clinical studies and breakthrough measurements over a 30-day period, and then another 75 times during the ensuing 18 days for test purposes. The yield of ^{178}Ta decreased from 44.6% to 21.1% over the 30-day clinical period and decreased to 16.4% at 48 days. The breakthrough ranged from 0.4 µCi to 3.7 µCi with a mean of 1.2 µCi over 48 days and 200 elutions. These results are

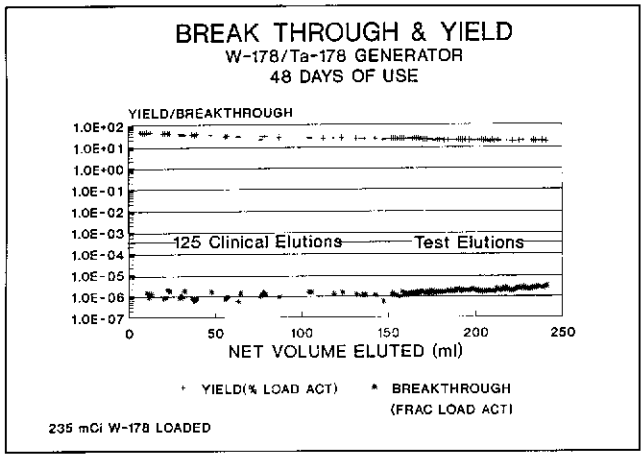

FIGURE 4. Breakthrough and yield performance of a large clinical generator loaded with 235 mCi ^{178}W clinically utilized for 30 days and tested for another 18 days.

similar to those obtained for manually-eluted generators which have been previously published. (*1*) From published radiation dosimetry estimates, the maximum whole-body doses from ^{178}Ta (99.5 mCi) and from ^{178}W breakthrough (3.7 μCi) were 51 mrem and 0.2 mrem, respectively (*1*). The portion of the dose from ^{178}W breakthrough, at the levels produced in this generator, is exceedingly small.

The detailed clinical results of the PTCA study are being prepared and will be published separately.

CONCLUSIONS

In summary, we have demonstrated that the new automated ^{178}W/^{178}Ta generator provides a safe, convenient, operator-independent source of ^{178}Ta with a safe shelf-life of at least 30 days. The system was successfully and extensively utilized in a very demanding portable procedure in the cardiac catheterization laboratory during coronary angioplasty. This demonstrated the rapidity of delivery, convenience of use, and portability of the system in a very practical application. Without these features, this study would not have been feasible. The enhanced features of this system should substantially facilitate first-pass radionuclide imaging with the multiwire gamma camera, both in standard clinical use and in research applications made possible by the unique features of the isotope and mobile multiwire camera.

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