Simple New Method for Effective Concentration of ^{188}Re Solutions from Alumina-Based ^{188}W–^{188}Re Generator

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^{188}Re is a useful generator-produced radioisotope currently under evaluation for a variety of therapeutic applications, including bone pain palliation and intravascular radiation therapy. Because the ^{188}W parent is available only in a relatively low specific activity (<0.15–0.19 GBq/mg) from reactor irradiation of enriched ^{186}W, relatively large volumes of 0.9% saline (>15 mL) are required for elution of the ^{188}Re daughter from traditional alumina-based ^{188}W–^{188}Re generators. Because these large bolus volumes result in solutions with a relatively low specific volume activity of ^{188}Re (<1 GBq/mL for the 18.5-GBq generator), the availability of effective methods for eluent concentration is important. Our new approach is based on the use of 0.3 mol/L ammonium acetate as a representative salt of a weak acid instead of saline for generator elution. **Methods:** After generator elution, the ammonium acetate generator eluent (15–20 mL) is passed through a tandem IC-H Plus cation (Dowex-H)–anion (QMA Light) column system. Exchange of ammonium cations with hydrogen ions on the cation column forms an acetic acid solution containing perrhenate anions from which the macroscopic levels of the acetate anion of the eluent have been effectively removed. Because perrhenic acid is fully dissociated at this pH, the QMA Light column specifically traps the ^{188}Re-perrhenate, which is subsequently eluted with a low volume (<1 mL) of saline. Concentration ratios greater than 20:1 are readily achieved with this method. **Results:** A typical clinical-scale generator loaded with 19.2 GBq ^{188}W was used to validate the approach. Saline elution provided ^{188}Re in a 75%–80% yield. Although elution with 0.15 mol/L NH_4OAc gave lower yields (55%–60%), use of 0.3 mol/L NH_4OAc provided yields comparable with those of saline (70%–75%). ^{188}W parent breakthrough was not detected after passage of the bolus through the tandem concentration system. Bolus volumes of 15–20 mL, which initially contained as much as 11.1–14.8 GBq ^{188}Re, were readily concentrated to less than 1 mL saline using QMA Light cartridges. The generator was evaluated for more than 3 mo with no decrease in performance. **Conclusion:** This approach represents a simple, rapid, and effective method using inexpensive disposable components of concentrating solutions of ^{188}Re for preparation of therapeutic agents.

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Radionuclide generator systems are often based on a chromatographic system in which the parent radionuclide is bound to a solid adsorbent. The parent is tightly bound with a high partition coefficient (K_D) to the adsorbent, which is usually housed in a chromatography column, and the radioactive daughter is continuously formed by decay of the parent. The radioactive daughter is removed by elution of the generator with an appropriate solution such as saline (*1*). Use of an appropriate adsorbent and eluent solution is required so that the daughter has a low K_D value and can easily be removed from the column by, for instance, passing through a solution (i.e., eluent) of physiologic saline (0.9% NaCl). In the case of reactor-produced ^{188}W (*2*), the parent radioisotope is produced with low specific activity (units of radioactivity per unit mass), which requires a large amount of adsorbent for binding. Even using the Oak Ridge National Laboratory high-flux isotope reactor, which has a high thermal neutron flux of more than 2×10^{15} neutrons/cm^2/sec, the irradiation of enriched ^{186}W targets for periods of 23–24 d (1 reactor operating cycle before refueling) provides ^{188}W with a relatively low specific activity of only 0.15–0.19 GBq/mg.

Because of the large amount of alumina adsorbent (>9 g) required to bind ^{188}W (14–27 MBq) for the traditional clinical-scale ^{188}W–^{188}Re generators (*3*), a large volume of solution (>15–20 mL) is required for elution of the daughter, which results in a solution of low specific volume activity, defined as the concentration of ^{188}Re per unit volume (MBq/mL). In the example of elution with a typical 18.5-GBq ^{188}W–^{188}Re generator at equilibrium conditions, the specific volume activity of the bolus can be as low as 0.74 GBq/mL. For subsequent chemical attachment of ^{188}Re to an agent for clinical use, concentrated solutions of the radioisotope are usually required. Methods for concentrating the solution are thus required. Our approach represents a simple, effective method for concentrating ^{188}Re solutions

obtained from ^{188}W–^{188}Re generators (*4–6*) to the high-specific-volume solutions that are required for applications such as the liquid-filled balloon approach for vascular radiation therapy after balloon angioplasty.

This strategy was developed because routine use of generators in general radiopharmacy or hospital settings requires simple solutions, and the only practical method for ^{188}W–^{188}Re generators thus involves elution of ^{188}Re with a salt solution. Whereas current methods for concentrating ^{188}Re solutions involve selective trapping of insoluble salts formed from the anion used for generator elution (e.g., AgCl (*7–8*)), our method is based on choosing a generator-eluting anion that forms a nonionized species after acidification. In this article, we describe the performance results from a typical clinical-scale ^{188}W–^{188}Re generator using this efficient method.

MATERIALS AND METHODS

All chemicals and reagents were of analytical grade unless otherwise indicated. The 97.5% enriched ^{186}W was purchased from Oak Ridge National Laboratory, and alumina acid grade (100–200 mesh) alumina (ICN, Irvine, CA) was used as the generator adsorbent. IC-H Plus cation exchange cartridges were purchased from Alltech Associates (Deerfield, IL), and QMA Light or amino (NH_2) SepPak cartridge ion exchange columns were obtained from Waters Corporation (Milford, MA). Generator columns were fitted with a coarse glass frit, and machined Teflon plugs (DuPont, Wilmington, DE) were fitted at either end with Luer Locks (Burron, Bethlehem, PA) (*3*).

Production and Processing of ^{188}W

^{188}W was produced by irradiation of enriched ^{186}W-oxide targets in the high-flux isotope reactor at a thermal neutron flux of 2–2.5 × 10^{15} neutrons/cm^2/sec (*3*). The targets were processed by dissolution in 1 N NaOH solution in the presence of hydrogen peroxide (*3*). The specific activity of the ^{188}W averaged 0.11–0.15 GBq/mg ^{186}W for a 1-cycle, 23- to 24-d irradiation. The reactor production and decay of ^{188}W are shown in Figure 1.

Radionuclide Analyses

Radioactivity measurements were determined using a calibrated high-purity germanium crystal solid-state detector (EG&G Ortec, Oak Ridge, TN) coupled to a personal computer–based multichannel analyzer (MCA) (Nuclear Data Inc., Schaumburg, IL; or Canberra, Meriden, CT). Samples of constant geometry were counted with low (<5%) dead time. Data were analyzed using Accu-Spec spectroscopy software (Nuclear Data). The MCA was calibrated using a calibrated radionuclide standard obtained from the National Institute of Standards and Technology, Gaithersburg, MD. Nuclear data were taken from the literature (*9*), and the radioisotope levels were determined by quantification of the following photopeaks: ^{188}Re, 155 keV (15%); ^{192}Ir, 316 keV (82.8%); and ^{191}Os, 129 keV (25.9%). The ^{188}W levels were usually quantified by measurement of the 155-keV γ-ray from decay of the ^{188}Re daughter in the ^{188}W–^{188}Re equilibrium mixtures. In some cases, direct measurement of the 227-keV (0.22%) and 290-keV (0.39%) γ-rays from decay of ^{188}W was possible after trapping of the ^{188}W generator column breakthrough on an alumina (neutral) SepPak (*10*). The dose calibrator (Capintec Inc., Ramsey, NJ) used for determining final ^{188}Re yields was calibrated with a secondary standard calibrated in the MCA.

Fabrication and Performance of Generator

After dissolution, the sodium tungstate solution was acidified to pH 2–3 with 1 N HCl and adsorbed onto a column of water-washed alumina housed in a lead shield. Generators were then conditioned by washing thoroughly with 100–200 mL 0.9% saline by gravity elution (*3*). Figure 2 illustrates the generator system housed in a lead shield. Because radiolysis from the high-radiation field can significantly reduce ^{188}Re elution yields, the aqueous solution was removed from the generator after daily use by simply passing air through the generator from a syringe at 1–2 mL/min.

Trapping and Elution of ^{188}Re-Perrhenate

For evaluation of the candidate materials for the ^{188}Re-perrhenate trapping column (Table 1), typically 370–3700 kBq (10–100 μCi) ^{188}Re-perrhenate in 10 μL saline were added to 2 mL distilled water and applied to anion exchange columns to trap the ^{188}Re-perrhenate anions. The columns were pretreated with 10 mL distilled water, and in the case of the SepPak, the column was pretreated with 10 mL 0.1 mol/L HCl followed by 10 mL water. The anion exchange columns had a typical bed volume of 0.5 mL. The columns were then eluted with 7 portions (2 mL each) of NaCl solution of increasing concentration (0.01, 0.05, 0.1, 0.2, 0.5, 1.0, and 2.0 mol/L). The activity of the eluents and the column was

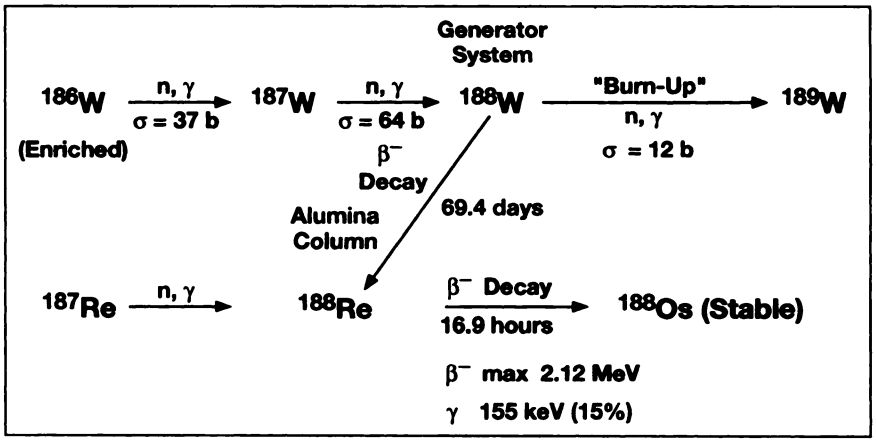

FIGURE 1. Diagram of production and decay of reactor-produced ^{188}W. Cross-section values (σ) are probabilities of neutron capture by target nuclei. Burn-up cross-section is neutron capture by product nucleus.

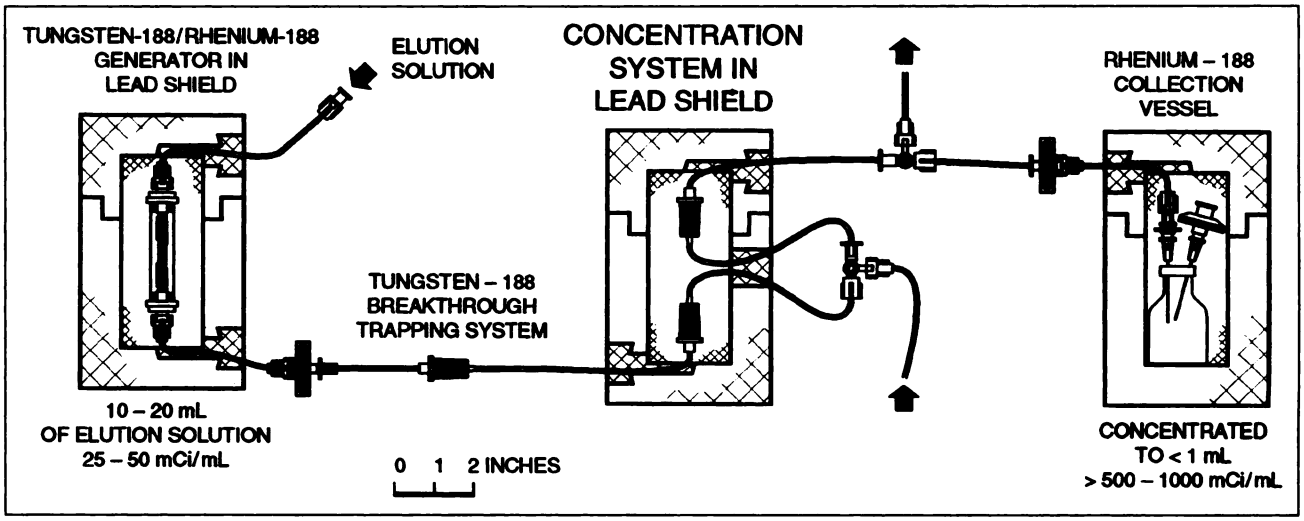

FIGURE 2. Illustration of alumina-based ^{188}W–^{188}Re generator with tandem IC-H Plus cation–QMA Light anion cartridge system. Generator column is housed in 2.5-cm-thick lead shield.

measured in a dose calibrator, and the percentages of activity in the eluents and on the column were calculated.

Elution of ^{188}W–^{188}Re Generators

To obtain baseline elution yields, the generators were initially eluted with 154 mmol/L (0.9%) saline at least 5 times during 2 wk before the eluent was changed to the desired 154 mmol/L ammonium or sodium salt solution of the following weak acids: ammonium ascorbate, ammonium borate, ammonium formate, ammonium acetate, ammonium propionate, ammonium lactate, sodium citrate, glycine, ϵ-aminocaproic acid, betaine, and sodium citrate (Table 2). The generators were eluted with a 20-mL volume and then purged twice with 20 mL air. The radiochemical yields were calculated with respect to the average baseline yield obtained with 154 mmol/L saline. In addition to the generator yield, bolus solutions obtained from the generators were concentrated and the radiochemical yields of ^{188}Re were calculated after elution from the QMA Light column.

Concentration of ^{188}W Bolus

The typical setup of the generator and the elution and concentration systems is shown in Figures 2 and 3. To minimize exposure, the system is constructed behind a leaded glass or plastic shield. A short length of disposable extension tubing is attached to the lower Luer Lock outlet connection of the generator. Inclusion of an in-line 0.22-μm filter (Millipore Corp., Bedford, MA) ensures trapping of any alumina fines or other particles that may be eluted from the generator. The in-line alumina SepPak also traps low levels of ^{188}W parent breakthrough (*10*). The tandem cation–anion concentration system (Fig. 3) consists of a commercially available IC-H Plus cation exchange cartridge with a capacity of 2–4 mEq attached to a 3-way stopcock connected at the outlet to the QMA Light cartridge. Another length of extension tubing then connects the outlet of the anion exchange column to the ^{188}Re collection vessel, which is housed in a leaded glass or plastic shield. With the stopcock open, the generator is eluted with 15–20 mL eluent at 1–2

TABLE 1
^{188}Re-Perrhenate Activity by Stepwise Elution of Different Anion Exchange Resins Using Series of Saline Concentrations

Saline concentration (mol/L)	Dowex 1 × 8	Dowex 2 × 8	Amberlyst A21	Amberlite IRA 416	QMA Light	SepPak NH_2
0	0.0	0.0	6.6	2.3	0.0	0.0
0.01	0.0	0.0	0.8	11.3	12.5	0.0
0.05	0.0	0.0	0.4	0.0	80.0	0.1
0.1	0.0	0.0	0.4	0.3	5.6	17.9
0.2	0.0	0.0	0.6	0.4	0.5	62.0
0.5	0.0	0.0	1.3	0.6	0.0	18.2
1.0	0.0	0.0	2.0	1.1	0.0	1.2
2.0	0.0	0.0	2.6	1.3	0.0	0.1
On column	99.9	99.9	85.3	82.7	0.0	0.4

Data are percentage of perrhenate adsorbed to different anion exchange materials with gradient of saline solutions of 2 mL each (resin bed volume, ~0.5 mL). Saline concentration of 0 mol/L is load of activity in 2 mL water and additional wash with 2 mL distilled water. Columns were pretreated with 10 mL distilled water or, in case of SepPak NH_2, with 10 mL 0.1 mol/L HCl followed by 10 mL distilled water. Dowex is manufactured by Sigma Chemical Co.; Amberlyst and Amberlite by Merck; and QMA Light and SepPak by Waters Corporation.

TABLE 2
Elution of ^{188}W–^{188}Re Generators Using Different Eluent Systems

Eluent (0.15 mol/L)	Eluent pH	Generator elution yield* (%)	% Eluted activity on QMA Light	Amount of eluant anion in final QMA Light eluate	Remarks
NH_4-formate	5.0	96 (±3)	91 (±5)	30 μmol or <0.26 μmol	Formate can be displaced by acetate if QMA is washed with acetic acid
NH_4-acetate	5.6	96 (±3)	96 (±3)	33 μmol	Determined quantitatively with ^{11}C-acetate
NH_4-propionate	5.1	93 (±2)	91 (±5)	Not detected	No significant observations different from acetate
NH_4-ascorbate	4.5	87 (±4)	96 (±3)	Not detected	Final eluate has yellow discoloration
NH_4-borate	6.5	Not detected	97 (±2)	Not detected	Leads to slow ^{188}W breakthrough
NH_4-lactate	4.5	Not detected	90 (±5)	Not detected	Leads to significant ^{188}W breakthrough
Na-citrate	4.5	Not detected	98 (±2)	Not detected	Leads to significant ^{188}W breakthrough
Glycine	6.0	Not reproducible (40–90)	91 (±5)	<0.3 μmol	Determined photometrically using triketohydrindene hydrate
ε-aminocaproic acid	6.3	87 (±2)	95 (±3)	Not detected	Yields decrease significantly if not eluted daily
Betaine	5.8	<2%	Not detected	Not detected	^{188}Re is not eluted from generator

*Relative to saline.
QMA Light is manufactured by Waters Corporation.

mL/min using a syringe or peristaltic pump. The initial eluent collected from the QMA Light column contains only low levels of radioactivity and is discarded. The stopcock is then adjusted to permit elution of the QMA Light cartridge with 5–10 mL distilled water. The ^{188}Re-sodium perrhenate is then obtained by elution of the QMA Light or SepPak trapping column with 0.9–1.0 mL 0.9% saline. The tandem cation–anion concentration system is used only once and discarded after use. The generator can be eluted every day because 65% of equilibrium levels of ^{188}Re are reached in 24 h (Fig. 4).

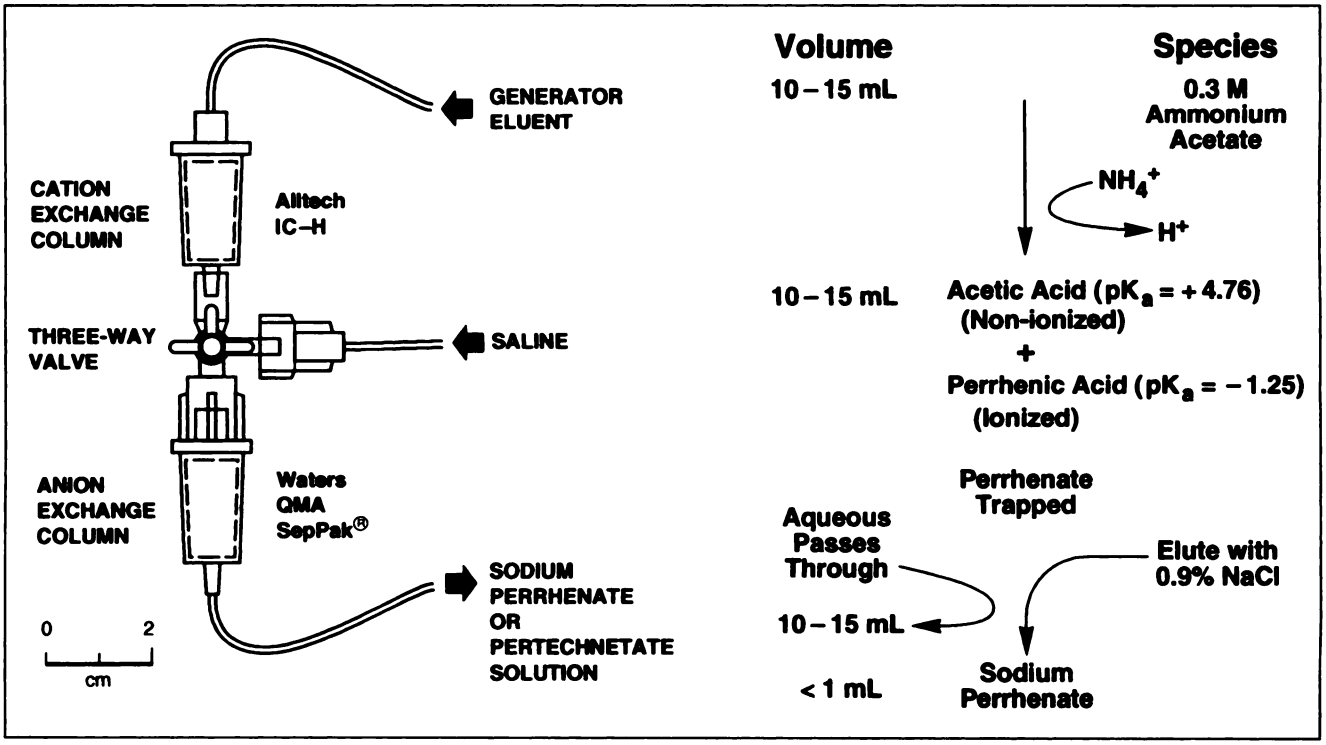

FIGURE 3. Detailed schematic of tandem IC-H Plus cation–QMA Light anion exchange system for eluent concentration. IC-H is manufactured by Alltech Associates, and QMA Light and SepPak are manufactured by Waters Corporation.

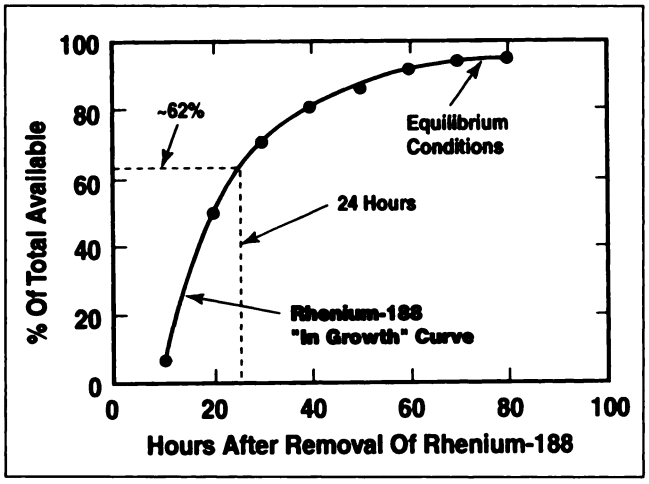

FIGURE 4. Curve illustrating ingrowth of ^{188}Re after removal of ^{188}Re bolus from ^{188}W–^{188}Re generator.

Quantitation of Acetate Levels with ^{11}C-Acetic Acid

The following procedure determined the level of acetate expected to be trapped in small amounts on the QMA Light anion exchange columns and eluted from the QMA Light trapping column with 1 mL 0.9% saline. Approximately 10 μL HPLC-purified ^{11}C-acetate solution (~500,000 cpm) were added to 20 mL 0.13 mol/L ammonium acetate solution. The ^{11}C-acetate tracer solution was then passed through the same column system of alumina, cation exchange, and anion exchange cartridges as was used for concentration of the ^{188}Re-perrhenate generator eluates. The QMA Light column was then disconnected from the other cartridges, washed with 5 mL distilled water, and eluted with 1 mL 0.9% saline. The levels of ^{11}C were then determined in the 20-mL waste fraction, in the 5-mL washing fraction, on the columns, and in the 1-mL saline eluate. Because the concentration and volume of the ^{11}C-acetate solution was known, this simple tracer method allowed us to determine the relative ratios of acetate and the quantitative and absolute levels of acetate in the individual fractions.

RESULTS

Our simple and easily adapted system works by elution of the ^{188}W–^{188}Re generator with a dilute ammonium or sodium salt solution of a weak acid (0.15 or 0.3 mol/L). The generator eluents are first passed through a strong cation exchange column (IC-H Plus). In this column the ammonium cations are exchanged for hydrogen ions. The resulting eluent from this column thus consists of ^{188}Re-perrhenate in an acidic solution. Because the weak acids are essentially not ionized at this pH, subsequent passage of the eluent through an anion exchange column (either QMA Light or SepPak) results in selective trapping of the perrhenate anion, with the bulk of the solution passing through as waste.

Table 1 summarizes the results of our studies with a variety of anion-trapping resins that were evaluated for their ability to reversibly bind perrhenate anions for a subsequent second elution with saline. The data show that the Dowex (Sigma Chemical Co., St. Louis, MO) and Amberlyst (Merck, Darmstadt, Germany) types of anion exchange resins are not suitable for this purpose under these conditions because anions are bound tightly and cannot be subsequently eluted even when using 2 mol/L saline; 80%–99.9% of the radioactivity is still bound to the columns. The only substance found to remove perrhenate on these types of resins was 2 mol/L nitric acid (*11,12*), which is not compatible with subsequent reductive labeling of radiopharmaceuticals. The commercially available SepPak, QMA Light, or amino column resins, however, bind the perrhenate with almost quantitative recovery of the ^{188}Re-perrhenate by elution with a small volume of saline. In our experience, the QMA Light cartridge is the best anion-trapping column, because re-elution is possible with low volumes of physiologic saline (<1 mL), whereas the amino type of column needs slightly higher saline concentrations (0.2–0.5 mol/L) or larger volumes for the elution. QMA Light was thus used as the anion-trapping column for all subsequent experiments.

After we identified QMA Light as optimal, we compared a variety of eluents with ammonium acetate. The eluents were used as 0.15 mol/L sodium or ammonium salt solutions (physiologic saline is 0.15 mol/L), with 0.15 mol/L saline serving as the baseline eluent for comparison of yields. The elution yields summarized in Table 2 are based on this eluent and show that our concept allows use of a wide variety of salts to elute the generators. Ammonium salts of formic acid, acetic acid, and propionic acid all worked well, with yields approximately 95% of those obtained with saline. These high yields remained constant for at least 4 wk with daily elutions (except on weekends).

The salts of ascorbic, boric, lactic, and citric acids were not as successful under these conditions. When ascorbic acid was used as the eluent, the eluate was discolored yellow, probably because of radiolysis with ascorbate on the generator column during recovery. Borate, lactate, and citrate solutions led to considerable breakthrough of ^{188}W, probably because of the chelating effects of these multifunctional acids. These eluents thus could not be considered selective for ^{188}Re, and longer term elution experiments were not performed, although initial elution yields of perrhenate were high (Table 2). The only alternatives to the simple alkanoic acids were solutions of simple amino acids such as glycine or ε-aminocaproic acid. As inner salts, the simple amino acids constitute the anion necessary to elute the perrhenate anion from the generator column. As cations, the simple amino acids are trapped on the cation exchanger after the generator column to decrease the ion concentration for successful trapping of perrhenate on the anion exchange column (Fig. 3). The elution yields obtained with these amino acids were similar to those obtained with acetate solutions, and ^{188}W breakthrough was not observed. However, initial elutions after changing the eluent from saline to the desired amino acid provided surprisingly low elution yields of ^{188}Re (<10%).

In these cases, the generator had to be eluted several times over several days with 100-mL portions of the eluent until

the radiochemical yields recovered to the values given in Table 2. Betaine (the trimethylammonium analog of glycine) did not provide significant elution yields. In the amino acid series, the long-chain ϵ-aminocaproic acid thus proved to be the best candidate evaluated, with the highest reproducibility and ^{188}Re yields. Some of eluents tested (lactate, citrate, and borate) led to significant breakthrough of the ^{188}W parent nuclide. Therefore, clinical use of these eluents must be strictly avoided. In studies using acetate as the eluent, the levels of ^{188}W breakthrough were quantitatively determined.

Long-term generator performance was evaluated with respect to ^{188}W breakthrough and ^{188}Re radiochemical elution yields. To determine whether the high radiation flux in a clinical-scale generator would affect elution yields, the 19.2-GBq (520-mCi) generator was eluted daily for 2 mo using ammonium acetate as the eluent (Fig. 5). From this generator, the average ^{188}Re yield with 0.15 mol/L ammonium acetate was approximately 75% of the initial yields obtained with saline. However, these preliminary studies using 0.3 mol/L acetate provided similar and even higher yields than the yields obtained with physiologic saline. The results of this detailed study clearly established acetate as an effective eluent for alumina-based ^{188}W–^{188}Re generators.

In some cases, the final saline eluates from the QMA Light columns (1 mL) were tested for their anion content from the initial (acetate, formate, and glycine) eluent after washing of the anion column with distilled water. The absolute amounts were found to be 30 μmol when formate was used as the generator eluent and 33 μmol when 0.3 mol/L acetate was used. When glycine was used, the absolute amount was even less than 0.3 μmol, probably because the cation exchange column strongly traps glycine but allows formate and acetate to pass through in the form of protonated acids. The levels trapped on the QMA Light cartridge are therefore higher. Thus, compared with glycine, 10-fold higher amounts of perrhenate are trapped as anions on the QMA Light cartridge as a result of dissociation. However, these levels do not represent a significant fraction of the total ^{188}Re-perrhenate recovered from the QMA Light column.

DISCUSSION

Concentration of ^{188}Re solutions requires the availability of a simple and efficient method that essentially involves selective separation of microscopic levels (no carrier added) of 1 anion (i.e., the desired ^{188}Re-perrhenate, obtained carrier-free or at least at subnanomolar ranges) from macroscopic levels of a second anion (i.e., from the salt solution used for generator elution). We reasoned that an anion with an ionization potential (pKa) that results in, practically, nonionization after passage through a strong cation exchange column in protonated form could be chosen for generator elutions (*4–6*). Thus, no anion would be competing with binding of microscopic levels of the perrhenate anion for selective trapping on the anion exchange column.

These methods are required for the use of ^{188}Re for various therapeutic applications. Research with this radioisotope has rapidly progressed over the last few years in both animal studies and clinical applications as a result of the ready availability of ^{188}Re from the ^{188}W–^{188}Re generator system, its long useful shelf-life, and the attractive radionuclide properties and versatile chemistry of rhenium. In addition to the recent use of ^{188}Re liquid-filled balloons for restenosis therapy (*13–17*), the use of ^{188}Re-HEDP (*18–21*) and ^{188}Re-(V)-DMSA (*22*) for palliation of bone pain is being pursued at several institutions. Other recent studies have described the development of ^{188}Re-labeled particles for intratumoral radiotherapy (*23–27*) and the evaluation of ^{188}Re-labeled antibodies (*28–31*) and peptides (*32–34*) for tumor therapy. The ^{188}W–^{188}Re alumina-based generators are routinely available from the Oak Ridge National Laboratory and are fabricated with ^{188}W produced in the high-flux isotope reactor. In addition to that reactor, reactors in Mol,

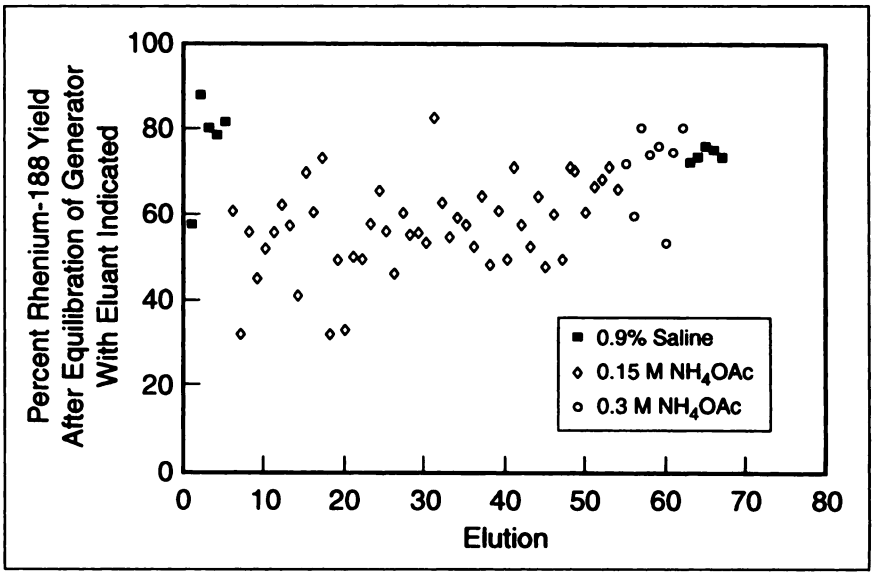

FIGURE 5. Radiochemical yields obtained with daily elutions of 19.2-GBq ^{188}W–^{188}Re generator using saline and acetate.

Belgium, and Dimitrovgrad, Russia, are capable of producing ^{188}W with a sufficiently high specific activity for these generators, and an alternative gel-type generator has been described (*35*).

Therapeutic applications require routine availability of ^{188}Re with a specific volume sufficient for the common relatively low-volume, high-activity radiolabeling procedures. Our new approach shows a unique application of postcolumn elution concentration: trapping carrier-free levels of perrhenate anions in selective anion exchange columns in the presence of weak acids for concentration of ^{188}Re-perrhenate solutions obtained by elution of ^{188}W–^{188}Re generators. The tandem system is based on initial generator elution with the ammonium or sodium (cation) salt of acetic acid (or other weak organic acids). Passage of the generator eluent through a cation exchange column in protonated form exchanges the ammonium cations for hydrogen ions, thus forming a weak acetic acid (or other weak acid) solution containing perrhenate ions. Subsequent passage of this weak acid solution through an attached anion exchange column selectively traps the perrhenate anion, because the weak acid is ionized to approximately only 0.01% of the acetate anion. The anions from the eluate are thus removed and are not available to compete with the perrhenate anion for binding to the anion exchange column. The perrhenate is then readily removed from the anion exchange column by elution with a small amount (<1 mL) of physiologic saline solution.

The unique features and advantages of our approach include an inexpensive, efficient, and simple system that can easily be sterilized for 1-time use. The final saline elution solution for QMA Light is physiologically compatible, and no excipients or additional chemical species are required, because the solutions contain only the carrier-free ^{188}Re perrhenate. In addition, the system is expected to easily be automated for concentration of perrhenate solutions. High specific volumes are required for high reproducibility of many radiolabeling procedures, such as the use of ^{188}Re liquid-filled angioplasty balloons for vascular radiation therapy after percutaneous transluminal angioplasty for restenosis therapy (*13–17*). The availability of such an efficient and inexpensive method would also extend the useful shelf-life of the generator. Our goal, therefore, was to develop a fast and simple concentration method suitable for routine clinical applications using sterile and disposable concentrator components.

Concentration requires the availability of effective and simple methods for the separation of large, macroscopic levels of anions from the generator eluent (i.e., chloride) from carrier-free levels of anionic radionuclides (i.e., perrhenate). Using salts of weak acids (e.g., ammonium acetate) as the generator eluent and using the carboxylate anion, instead of the usual chloride anions, as the actual eluting species take advantage of the large differences in pKa values of weak carboxylic acids (in the range of 3–5) compared with the strongly acidic pertechnic or perrhenic acid (0.3 and −1.25, respectively) (*36*). Our method provides perrhenate in a chemical form (i.e., physiologic saline solution), which is the formulation of choice for radiolabeling clinical agents. The method will allow clinical application of ^{188}W–^{188}Re generators, especially using the dilute solutions of ^{188}Re that result from the low-specific-activity ^{188}W produced by low-flux reactors.

Any significant ^{188}W-parent breakthrough, which has not been previously observed even without a concentrating unit (i.e., ~0.0001%/bolus), is eliminated with this tandem system. Any trace of tungsten removed from the generator column during elution either is trapped on the subsequent alumina or ion exchange columns or, if uncharged, is discarded with the waste. Thus, the tandem system not only fulfills the most important concentration role but also increases the radiochemical purity of the generator eluates.

Our approach is also effective for concentration of ^{99m}Tc-pertechnetate solutions (*37,38*) obtained from ^{99}Mo–^{99m}Tc generators fabricated from low-specific-activity $^{98}Mo(n,\gamma)$-produced ^{99}Mo. Initial data from elution of 37-GBq commercially available ^{99}Mo–^{99m}Tc generators with 0.3 mol/L ammonium acetate solution clearly show that in complete analogy to the ^{188}W–^{188}Re-generator, bolus volumes as high as 20 mL can easily be reduced to a volume of 1 mL by applying the cation–anion tandem system for ^{188}Re (*6*). The radiochemical yield of the generator elution was comparable with that of saline (>90%), and the losses of ^{99m}Tc on the concentrating unit were less than 2%. This method also represents a way to use neutron-activated ^{99}Mo as an alternative to fission-produced ^{99}Mo, which has the distinct disadvantages of requiring highly enriched uranium and specialized facilities, and an opportunity to extend the shelf-life of ^{99}Mo–^{99m}Tc generators, thus reducing costs.

Low-specific-activity generators can be obtained by, for example, (n,γ)-reaction on ^{98}Mo. Obtaining high-specific-volume solutions from such low-specific-activity generators requires special postelution concentration techniques. Reported examples involve sublimation (*37*), solvent extraction (*38*), and solution chemistry. Generator-based solution chemistry with disposable units for concentration is, in our opinion, attractive for clinical use because of ease, safety, and sterility.

CONCLUSION

Using solutions of salts of weak acids as eluents for high-bed-volume ^{188}W–^{188}Re generators prepared from low-specific-activity ^{188}W is highly reproducible and efficient. Many systems of weak acids can be applied, allowing optimization of radiochemical yields and parent breakthrough. This method allows reduction of boluses with volumes greater than 100 mL to volumes of physiologic saline less than 1 mL. The method is easy; employs nontoxic, sterilizable, and disposable materials for single use; and is therefore easily applicable to clinical nuclear medicine.

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