

Tantalum-178—A Short-Lived Nuclide for Nuclear Medicine: Development of a Potential Generator System

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We describe a chemical separation that may form the basis of a generator system for the short-lived radionuclide Ta-178 ($T_{1/2} = 9$ min). The parent nuclide W-178 ($T_{1/2} = 21.7$ days) is loaded on an anion-exchange column and the daughter eluted with a mixture of dilute hydrochloric acid and hydrogen peroxide. The yields of tantalum and the breakthrough of the tungsten parent as a function of the eluting conditions are discussed, and preliminary animal distribution data are presented for various treatments of the eluant solution.

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The preceding paper in this issue of the *Journal* (1) describes the cyclotron production of tungsten-178, the parent of tantalum-178—a short-lived, low-energy gamma emitter. The present communication reports on the development of a separation of the daughter isotope that may be suitable as a generator system for this radionuclide pair.

Tantalum shows strong tendencies toward colloid formation, and true solutions can be obtained only by the use of complexing agents such as fluoride or oxalate ions or mixtures of such agents (2–8). Unfortunately such solutions are not usually suitable for i.v. administration. The separation described here is based on the adsorption of W-178 as tungstate on an anion-exchange column, with elution of tantalum by solutions of dilute hydrochloric acid containing low concentrations of hydrogen peroxide.

MATERIALS AND METHODS

Isolation of W-178. The carrier-free separation of tungsten from the irradiated tantalum targets was carried out by anion-exchange chromatography in a mixture of hydrochloric and hydrofluoric acids (9). The irradiated portions of the tantalum target foils were cut out and dissolved in concentrated hydrofluoric acid to which concentrated nitric acid was added in drops until a clear solution was obtained.

The solution was evaporated to dryness, the residue taken up in concentrated hydrochloric acid and again evaporated to dryness. The resulting material was redissolved in 6N HCl–1.5N HF solution (10 ml/100 mg tantalum) and refluxed for 30 min to ensure that less than 0.1% of the tantalum remained in colloidal form.

A 200–400 mesh anion-exchange column*, 1 cm in diameter and with a height of 3 cm/100 mg tantalum (minimum height 10 cm), was equilibrated with 6N HCl–1.5N HF solution and the target solution eluted through the column. Only tungsten-178 was detected in the eluant. By continuing the elution with another six column volumes of fresh 6N HCl–1.5N HF, 98% of the W-178 was collected.

Separation of Ta-178 from W-178. The tungsten solution obtained above was evaporated to dryness and the residue taken up in 0.15N HCl–0.1% H_2O_2 solution. This was percolated through a pre-equilibrated 200–400 mesh anion-exchange column in order to load the tungsten parent. During the initial stages of development a 9-ml resin bed was used.

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VARIATION OF ^{178}Td YIELD WITH
HYDROCHLORIC ACID CONCENTRATION
(0.05% H_2O_2 , BIO-RAD AG 1 x 8)

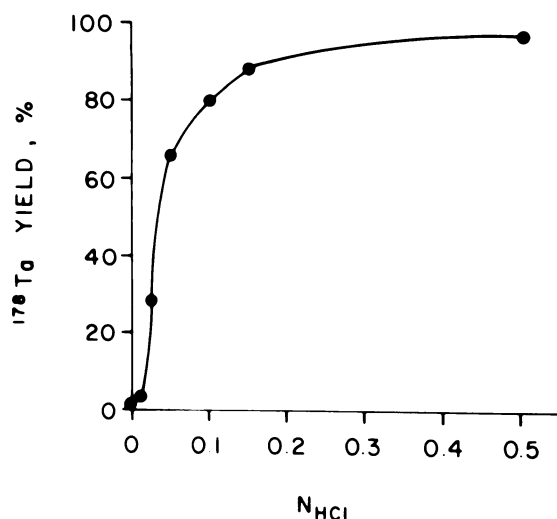


FIG. 1. Tantalum-178 yield (in percentage of theoretical maximum) as a function of HCl concentration. H_2O_2 is constant at 0.05%.

^{178}Td ELUTION PROFILE (9 ml COLUMN)

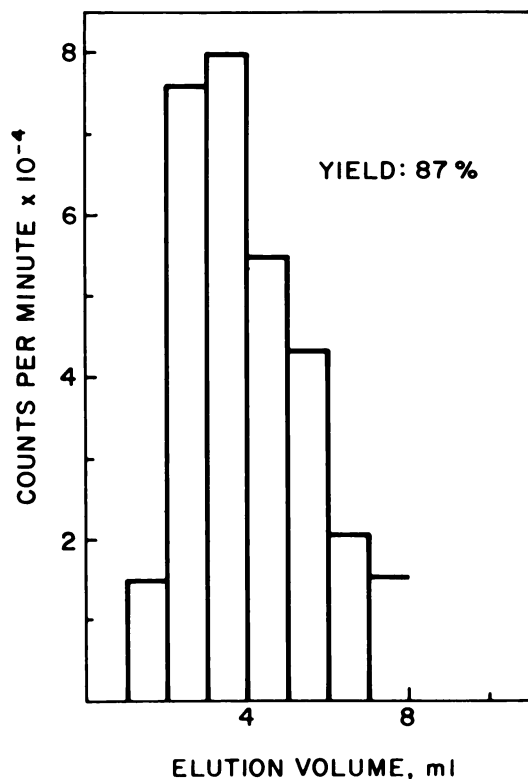


FIG. 2. Typical elution profile obtained with 9-ml volume resin bed eluted with 0.15N HCl-0.05% H_2O_2 .

In order to test for the optimum yields of Ta-178, eluting solutions were used ranging from 0 to 1N in hydrochloric acid and 0 to 0.2% in peroxide. All samples were counted on a NaI(Tl) detector and the half-life and purity of the eluted activity determined in each case. Breakthrough of the tungsten parent was determined under each of the eluting conditions. High-resolution gamma-ray spectra of the eluted samples were obtained using a 0.6-cc wafer Ge(Li) detector.

In addition, the distribution constants (K_D) of tungsten and tantalum between the anion-exchange resin and the various mixtures of HCl and H_2O_2 were investigated by batch equilibration. The K_D was calculated from the expression $\frac{\% \text{ metal/g resin}}{\% \text{ metal/g liquid phase}}$. The radioactive tracers used in these studies were W-178, Ta-178, and Ta-182.

In order to reduce the volume of eluant from the generator to levels more acceptable for i.v. injection, the resin-bed volume was reduced in later experiments to a maximum of 1 ml. Yields of tantalum and tungsten breakthrough were determined in the same way as for the larger columns.

Animal distribution studies. Preliminary biodistribution studies were performed in rats at 15–20 min after i.v. administration of one column volume of Ta-178 eluant (0.1N HCl — 0.1% H_2O_2) from the 0.6-ml column, typically using 50 μCi of the radio-nuclide. Further studies were carried out using eluant solutions adjusted to pH 7 with 4.06% $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ and to pH 5.4 with 3.03% citrate buffer. The effect of carrier on both tantalum and tungsten distributions was determined using solutions containing Ta-182 and W-181 as tracers. Ten μg of tantalum and 5 μg of tungsten were injected in these experiments.

RESULTS

Separation of W-178. Elution of the 6N HCl — 1.5N HF target solution through the anion-exchange resin gave a 98% yield of carrier-free tungsten, with 99.9% of tantalum retained on the column. The remaining 0.1% of the tantalum was eluted before the tungsten, so that this colloidal tantalum could also be separated from the W-178. The refluxing step described in the procedure is important to minimize the level of this colloidal tantalum.

Separation of Ta-178 from W-178. The use of varying mixtures of hydrochloric acid and hydrogen peroxide to elute the generator column showed that the yields of tantalum were essentially independent of peroxide concentration, but that breakthrough of the tungsten was inhibited by the presence of peroxide in the eluting solution.

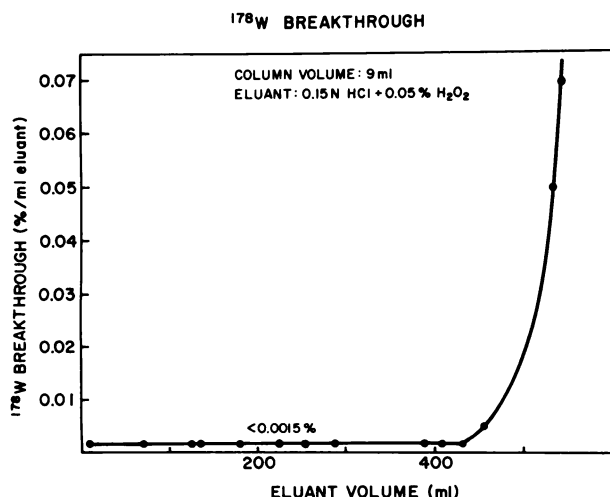


FIG. 3. Breakthrough of W-178 as a function of eluant volume (9-ml resin bed, 0.15N HCl-0.05% H_2O_2).

Figure 1 shows the variation of tantalum yield, as a percentage of the theoretical maximum, with the concentration of hydrochloric acid in the eluant, using a constant level of hydrogen peroxide (0.05%). Clearly a minimum concentration of 0.05N HCl is required for reasonable yields of the tantalum daughter.

Figure 2 shows a typical elution profile for Ta-178 from a 9-ml resin bed percolated with a solution of 0.15N HCl — 0.05% H_2O_2 . Approximately 88% of the eluted activity appears between the second and sixth milliliter of eluant, while one column volume collects 87% of all Ta-178 originally in equilibrium

VARIATION OF ^{178}W DISTRIBUTION COEFFICIENT WITH HYDROCHLORIC ACID CONCENTRATION BIO-RAD AG 1x8 (200-400 mesh)

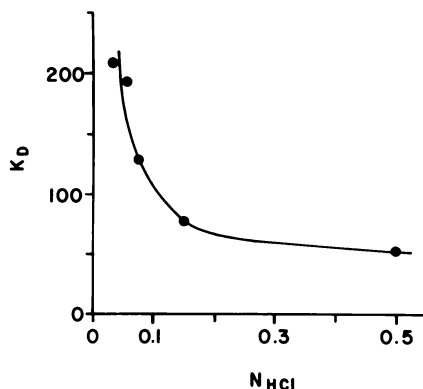


FIG. 4. Variation of W-178 distribution coefficient between Bio-Rad AG 1-X8 resin and various concentrations of hydrochloric acid. Each solution contained 0.05% H_2O_2 in order to stabilize any tungsten on resin material.

with the W-178. Although the peak profile is sharp, some tailing of the tantalum activity is evident.

Figure 3 shows the behavior of the W-178 adsorbed on a 9-ml column eluted with the 0.15N HCl — 0.05% H_2O_2 . Up to a volume of approximately 420 ml, the level of tungsten breakthrough, expressed as a percentage of the tungsten loaded on the column, lies below the detection limit imposed by the experimental conditions (0.0015%), and after 500 ml it becomes appreciable (ca. 0.05%). Table 1 shows the variation of W-178 breakthrough observed in one column volume as a function of hydrochloric acid normality and the proportion of hydrogen peroxide. The results using 1N HCl clearly show the need for peroxide in the eluting solution, with 0.005% reducing breakthrough from 1.7%/ml to 0.03%/ml. It appears that a minimum of 0.05% is required to bring breakthrough to acceptably low levels. A comparison of the breakthrough figures obtained with distilled water and 1N HCl shows that W-178 is released significantly more easily as the hydrochloric acid normality is increased.

This finding is underlined by the W-178 batch equilibration results shown in Fig. 4. At a constant level of 0.05% H_2O_2 , the distribution coefficient K_D decreases markedly with increasing normality of the HCl. Similar Ta-182 tracer studies again showed the lack of dependence of tantalum K_D values on peroxide concentration, and a dependence on the normality of the HCl of the type shown in Fig. 1. The necessity for the presence of H_2O_2 was demonstrated in one column loaded with W-178 and eluted with 0.15N HCl. Early breakthrough of tungsten was detected. Changing the eluant to 0.15N HCl — 0.05% H_2O_2 led to no further detectable losses of tungsten until very large volumes of eluant had been percolated through the column.

With the columns having a 0.6-ml resin bed, it was decided to use an eluant consisting of 0.1N HCl and 0.1% H_2O_2 , because of the higher K_D value of tungsten in the more dilute HCl solution, and because of the more effective stabilization of tungsten by the higher level of hydrogen peroxide. The overall tantalum yield under these conditions was 74% per column volume. The elution profile for this size of column typically showed the integrated yield to be 75% of the total in the first 0.4 ml and 80% in the first 0.6 ml of eluant. Continuous elution of this column showed a level of 0.01% W-178 breakthrough per milliliter after approximately 80 column volumes. The compromise between tungsten breakthrough and tantalum yield is illustrated by the fact that elution of this column with 0.05N HCl — 0.05% H_2O_2 solution allows double this number of column volumes to be passed before this level of break-

TABLE 1. VARIATION OF W-178 BREAKTHROUGH WITH HYDROCHLORIC ACID CONCENTRATION AND PERCENTAGE OF HYDROGEN PEROXIDE

N _{HCl}	% H ₂ O ₂	% W-178 breakthrough
0	0	<0.001*
	0.05	<0.001
0.01	0.05	<0.001
0.025	0.05	<0.001
0.050	0.05	<0.001
0.15	0.05	<0.001
1.00	0	1.7
	0.005	0.03
	0.05	0.008
	0.20	<0.005

* % breakthrough

$$= \frac{\text{W-178 breakthrough/ml eluant}}{\text{W-178 added to the column}} \times 100.$$

TABLE 2. DISTRIBUTION IN RATS OF CARRIER-FREE Ta-178 SOLUTIONS 15-20 MIN AFTER I.V. ADMINISTRATION

	Ta-178 eluate in 0.1N HCl- 0.1% H ₂ O ₂	Carrier-free Ta-178 in phosphate buffer pH 7.0	Carrier-free Ta-178 in citrate buffer pH 5.4
Blood	51.0*	37.0	20.0
Liver	4.0	13.0	2.5
Lungs	1.2	1.0	1.0
Spleen	0.4	0.5	0.1
Heart	0.7	0.4	0.3
Kidneys	0.8	1.7	1.2
Muscle	13.0	11.0	16.5
Bone	10.0	4.0	11.0
Skin & fat	7.0	8.0	20.5
Urine	6.0	7.0	15.0
Recovery	94.1	83.6	88.1

* Percentage of injected dose per organ, an average of five animals.

through occurs. The tantalum yield, however, is reduced to 66% under these conditions.

Figure 5 shows a typical gamma-ray spectrum of the eluted Ta-178, obtained with a Ge(Li) detector. Comparison of this spectrum with that in Fig. 3 of the preceding paper shows the absence of characteristic tantalum radiation produced as a result of the electron-capture decay of the parent W-178.

Animal studies. Table 2 shows the organ distribution of Ta-178 (eluted with 0.1N HCl — 0.1% H₂O₂) at 15-20 min after i.v. administration. In the first column the results are those for the unmodified eluant, in the second for eluant adjusted to pH 7 with phosphate buffer, and in the third for solution treated with citrate buffer (pH 5.4). The most significant differences between the three carrier-free tantalum

preparations lie in blood, liver, skin, fat, fur, and urine levels.

The effects of added carrier on the distribution of tantalum and tungsten solutions are shown in Table 3. The first two columns give the results obtained with Ta-182 solutions at pH 7 (phosphate buffer) and pH 5.4 (citrate buffer). Liver activity levels are somewhat lower in the case of the citrate solution, but skin, fat, and fur are higher. Comparisons with the corresponding carrier-free results in Table 1 indicate no essential differences in either case. The carrier phosphate Ta-182 solution has somewhat elevated bone and liver levels compared with the carrier-free preparation, but this could be due to increased sequestration of colloidal material at the late time of sacrifice (30 min).

The third and fourth columns in Table 3 show the results obtained with carrier solutions of W-181 and carrier-free solutions of W-178, both buffered to pH 5.4 with citrate. Again, no significant differences can be seen in the two distributions, the most salient feature of both being rapid clearance through the kidneys.

DISCUSSION

Ta-178, the short-lived daughter of W-178, has potential applications for radionuclide imaging using the high-atmosphere multiwire proportional counter (1). We have described a high yield (98%) carrier-free separation of the W-178 from tantalum foils after (p,4n) bombardment of Ta-181. Furthermore, the ion-exchange separation, which is the basis of the proposed generator system, gives good yields of

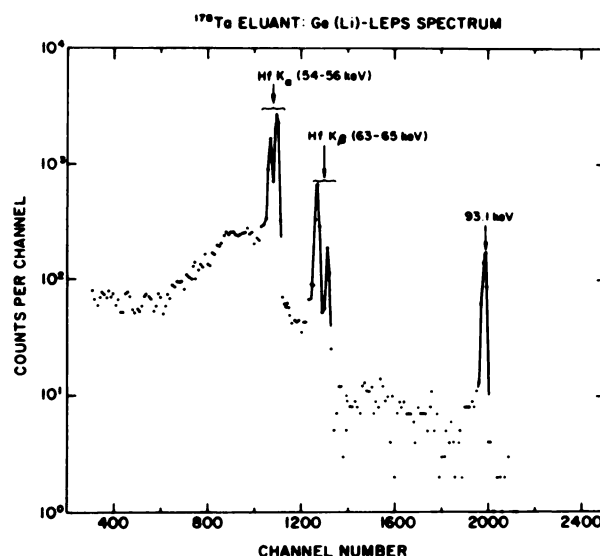


FIG. 5. Ge(Li) pulse-height spectrum from eluted Ta-178 solution. Note absence of tantalum characteristic radiation (cf. Fig. 3 in preceding paper).

TABLE 3. DISTRIBUTION IN RATS OF CARRIER W-181 AND Ta-182 AND CARRIER-FREE W-178 SOLUTIONS 30 MIN AFTER I.V. ADMINISTRATION

	Ta-182 & carrier in phosphate buffer pH 7.0	Ta-182 & carrier in citrate buffer pH 5.4	W-181 & carrier in citrate buffer pH 5.4	W-178 in citrate buffer pH 5.4
Blood	23.0*	25.3	4.9	2.7
Liver	19.4	8.5	5.6	4.4
Lungs	6.4	1.1	0.3	0.3
Spleen	0.8	0.1	0.1	0.1
Kidneys	3.1	1.2	2.8	2.5
Muscle	13.8	16.9	7.0	7.2
Bone	13.1	9.0	14.6	20.0
Skin & fat	9.5	21.6	12.2	7.0
Urine	4.1	8.0	44.0	50.0
Recovery	93.2	81.7	91.5	94.2

* Percentage of injected dose per organ, an average of two to three animals.

Ta-178 and acceptably low levels of parent breakthrough.

The recipe for generator elution is a compromise resulting from the required yield of tantalum and the number of elutions that may be made before W-178 breakthrough becomes unacceptable. Hydrogen peroxide is used to reduce W-178 breakthrough—presumably by maintaining the tungsten on the column in the form of tungstate. Although the concentrations of hydrogen peroxide used in this study did not produce observable physiologic effects, the hydrogen peroxide could be destroyed before administration by treating the eluant with sodium bisulfite.

Some tungsten breakthrough occurs immediately after loading the column and also after leaving the column standing for several hours. With an eluting solution of 0.1N HCl — 0.1% H₂O₂, no breakthrough higher than 0.1% is seen in the first eluted fraction after the column had been standing up to 1 wk. We, therefore, routinely discarded the first eluant. When the breakthrough from a particular column reaches high levels, the tungsten can be removed by elution with 10 ml of 11N HCl. This solution can then be evaporated to dryness, the residue redissolved in 0.1N HCl — 0.1% H₂O₂ and loaded onto a new pre-equilibrated resin bed. After percolating 3 ml of the latter solution through, the column is ready for use.

No attempt was made to identify the chemical form of the eluted tantalum. In dilute hydrochloric acid solution the metal is normally in colloidal form as a result of the formation of polynuclear complexes, but according to Kraus and Nelson (4), pentavalent tantalum adsorbs strongly on an anion-exchange

resin in dilute HCl solution. Under the conditions used here, the tantalum is evidently soluble or at least is in a form that has little affinity for the resin column; it is therefore possible that the species could be Ta(OH)₄⁺ and/or Ta(OH)₅. According to Babko et al. (10), these are the principal species at pH values lower than 2 in the absence of polynuclear complex formation. The variation in elution yields for tantalum appears to be in reasonable agreement with their reported values for the fraction of Ta(OH)₄⁺ existing in dilute acid solutions. The presence of two species in the eluant, presumably with differing affinities for the column material, could account for the tailing observed on the column. Some contribution would also be expected from the continued production of Ta-178 from its parent W-178 on the column. Batch equilibrium studies with different ratios for resin-to-liquid phase, however, indicate the presence of only one species.

Using Ta-182 as a tracer, the *K_D* for tantalum was determined to be less than 0.3 for equilibration between the 0.1N HCl — 0.1% H₂O₂ solution and the anion-exchange resin. On this basis it appears that all the tantalum should be eluted from the column. The fraction of Ta-178 retained at lower HCl concentrations may represent an unidentified tantalum species that coexists with carrier levels of Ta. The observation that a solution of Ta-182 containing Ta carrier has the same elution profile as the carrier-free Ta-178 supports this hypothesis. Addition of carrier tantalum did not alter the yields or the tailing effect, and neither did prolonged equilibration times in the batch studies. This seems to exclude the possibility of a slow reaction leading to the formation of a strongly adsorbed tantalum species.

The percentage of tantalum collected as a function of eluant acidity is in fair agreement with the fraction of Ta(OH)₄⁺ that would occur in a tantalum solution in the absence of polynuclear complexes (10). If two species did exist in solution, and if equilibrium were established quickly between them, then upon removal of either one, the yield of the species with low *K_D*, presumably Ta(OH)₄⁺, would reflect its ratio in the equilibrium mixture. The high-*K_D* species remaining on the column would then begin to re-establish the equilibrium so that tantalum would still be eluted giving rise to the observed tailing effect.

Whatever the nature of the eluted tantalum, it appears to show reactivity as evidenced by the dependence of animal distributions on the treatment of the eluted solution. Given the half-life of 9 min, radioactive agents could be produced if the chemical manipulations were rapid enough. At this stage, however, we plan to investigate the compatibility of the radionuclide with a prototype low-energy multiwire

proportional camera with ultimate applications to dynamic cardiovascular imaging.

FOOTNOTE

* Bio-Rad AG 1-X8.

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