A New Osmium-191/Iridium-191m Radionuclide Generator System Using Activated Carbon

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A new osmium-191/iridium-191m ($^{191}Os/^{191m}Ir$) radionuclide generator system has been developed based on the adsorption of K_2OsCl_6 (Os-IV) on 140-230 mesh heat-treated activated carbon. The generator is eluted with pH 2 saline solution containing 0.25 g/l KI to give ^{191m}Ir in good yield. The generator eluent is neutralized to physiologic pH and isotonicity with Tris buffer immediately prior to i.v. injection. No scavenger column is required. As an example, elution of the prototype generator with a 2-ml bolus results in elution of ^{191m}Ir in ~18% yield with an ^{191}Os breakthrough of only 2×10^{-4}%/bolus. The prototype generator has consistent performance over a 2-wk period with no change in ^{191m}Ir yield or ^{191}Os breakthrough. Loading of up to 1.5 Ci of ^{191}Os results in no observed radiolysis. Continuous elution of this system is also possible with a mean ^{191m}Ir yield of 3.7%/ml and a mean ^{191}Os breakthrough of 2×10^{-5}%/ml at a flow rate of 12 ml/min. This new system represents a readily available source of ^{191m}Ir for radioangiography. Adsorbed radiation dose calculations indicate a total-body dose of only 3.9 mrad for a 100 mCi injected bolus.

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Iridium-191m (^{191m}Ir) (4.96 sec) is obtained from an osmium-191 (^{191}Os) (15 days-β^- decay) generator and emits x-rays (63 keV-16%, 65 keV-28%, 74 keV-12%) and a gamma-photon (129 keV-26%) that can be detected with conventional gamma cameras. The very low radiation dose and opportunity to perform rapid, repeat studies make this system very attractive in comparison to other single photon generator-derived radionuclides that are available for radionuclide angiography (*1,2*). A description of an $^{191}Os/^{191m}Ir$ separation by ion exchange techniques was published in 1956 (*3*). Later, a generator designed for medical purposes was developed which used the AG1X8 anion exchanger resin as $OsCl_6$ ions adsorbent but this system was not pursued for clinical studies (*4,5*). Hnatowich et al. described a generator constructed by adsorption of hexachloroosmate on AG1X4 resin in which ^{191m}Ir was eluted with a solution of 8.7% NaCl at pH 2.2 (*6–8*). The latest design of this generator, first described in 1980, employs the AGMP-1 resin loaded with osmium(VI) (*9,10*) that utilizes a pyrocatechol "scavenger" column to trap the majority of the ^{191}Os breakthrough. Iridium-191m obtained from this system has been used effectively for the evaluation of intracardiac shunts in children (*11,12*) and for the determination of left ventricular ejection fraction in adults (*13,14*). An alternative generator system incorporating malonic acid in the eluent solution was recently described by Packard et al. The system showed good ^{191m}Ir elution yield (30–35%) and low ^{191}Os breakthrough (3×10^{-3}%) but the authors observed a more rapid decrease of the yield as a function of the time than with the previous system (*15*).

Because of the rather complicated fabrication of the AGMP-1 generator system and the relatively short useful life due to decreasing ^{191m}Ir yields and increasing ^{191}Os breakthrough (*9*), other potential $^{191}Os/^{191m}Ir$ generator systems have been evaluated. Since ^{191}Os is reactor produced, and has a 15-day half-life, these

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generators could be available at a reasonable cost with a shelf-life of 2–3 wk if the problems of increasing ^{191}Os breakthrough and rapidly decreasing ^{191m}Ir yields could be overcome. Recently, we evaluated 39 exchangers and carbon was the most promising (*16–18*). The goals of the present studies were to evaluate carbon absorbent systems in more detail and to develop a new carbon-based generator to achieve higher yields of ^{191m}Ir and lower ^{191}Os breakthrough over a period of several weeks without the necessity of a second ^{191}Os "scavenger" column.

MATERIALS AND METHODS

Osmium-191 Production and Processing

Osmium-191 was prepared by neutron irradiation of isotopically enriched (97.8%) granulated metallic osmium in the Oak Ridge National Laboratory High Flux Isotope Reactor (HFIR) with subsequent fusion in a mixture of KOH-KNO_3 (*9*). The effects of irradiation period on the levels of ^{191}Os, ^{191m}Ir, ^{191}Ir, ^{192}Ir, ^{185}Os have been discussed in detail in an earlier study (*19*). The production of ^{191}Os is experimentally linear for 6 days of irradiation before production yields deviate from proportionality with time. For routine production, a 3-day irradiation period at a flux of $\sim 2.5 \times 10^{15}$ $n/cm^2 \cdot sec$ compromises between yields of ^{191}Os and the increased formation of undesirable radionuclide impurities. Under these experimental conditions, the production yields per mg of enriched 97.8% ^{190}Os are as follows: ^{191}Os, 248 mCi; ^{193}Os, 5 mCi; ^{192}Ir, 0.4 mCi; and ^{194}Ir, 0.4 mCi. The critical radiochemical impurity is ^{192}Ir since ^{193}Os and ^{194}Ir rapidly eliminate by decay. The presence of ^{192}Ir in the eluate from $^{191}Os/^{191m}Ir$ generators has recently been discussed (*20,21*). After fusion, the irradiated target is dissolved in water to give an ~0.4 N KOH solution of potassium perosmate-(VIII), $K_2[OsO_4(OH)_2]$ (Fig. 1), which is mixed with two volumes of ethanol to reduce the Os(VIII) to Os(VI). After 10 min, five volumes of concentrated hydrochloric acid are added quickly, and the solution is heated in a boiling water bath for 30 min. The solution is then evaporated to dryness, and the brick-red precipitate of K_2OsCl_6 dissolved in 0.9% NaCl-0.01 N HCl. The kinetics of potassium tetrachloroosmate(VI) reduction in concentrated HCl during heating with alcohol can be followed spectrophotometrically. The 370 nm absorbance corresponding to the maximum of a peak characteristic of K_2OsCl_6 (*22,23*) reaches its maximal value after 15 min and remains constant up to 5 hr. The use of an ^{191}Os solution of perosmate demonstrated quantitative conversion to K_2OsCl_6. No loss is detected during the evaporation step, confirming the results obtained by other authors (*24*) concerning the evaporation HCl solutions of K_2OsCl_6 of different concentrations.

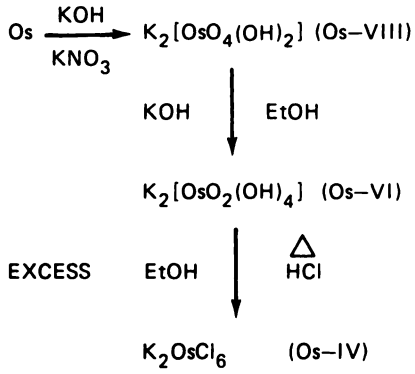

FIGURE 1
Preparation of K_2OsCl_6 (Os-IV)

Preparation of Activated Carbon Adsorbent

Earlier studies suggested that activated carbon was a good candidate for evaluation as an exchanger for the $^{191}Os/^{191m}Ir$ system (*16–18*). A variety of sources of carbon were evaluated. The carbons were pulverized in a mortar and pestle and sieved through U.S. standard sieves.* The 140-230 mesh fraction was chosen for evaluation since it represented a compromise between sufficient surface area for good ^{191}Os binding and rapid ^{191m}Ir release, and a pressure that did not interfere with rapid (≤1 sec) elution. For our new prototype generator, 140-230 mesh "activated carbon,"† was heated for 4–6 hr at 800–900°C under a stream of argon which effectively removed large amounts of KI and I_2 and destroyed the oxygen surface functional groups.

Comparison of Elution Characteristics of Various Activated Carbons

Seven commercially available activated carbon products of different sources were evaluated as potential adsorbents for the $^{191}Os/^{191m}Ir$ generator system. The carbons (140-230 mesh) were slurried in distilled water and loaded into 1 ml syringes‡ plugged with glass wool. Ten millicuries of a solution of freshly prepared K_2OsCl_6 was loaded on each column by means of a pump at a flow-rate of 1 ml/hr. The columns were then washed with 20 ml of pH 2-0.9% NaCl solution at 3 ml/hr. The choice of the nature of the eluting solution has been described in a previous study (*16*). Samples of the fixation and wash solution were counted to determine ^{191}Os fixation and ^{192}Ir elution percentage. The columns were washed manually with 50 ml of pH 2-0.9% NaCl and yield and breakthrough then measured using a 5-ml bolus (Table 1).

Fabrication and Elution of Prototype Generator

The 140-230 mesh heat-treated carbon (0.75 g) was slurried in distilled water and washed successively until the decanted solution was clear. The carbon slurry is added to a plastic 2-ml syringe and plugged with fine

TABLE 1
Summary of Properties of Different Sources of Carbon as Adsorbents for $^{191}Os/^{191m}Ir$ Generator System

Carbon	Source	Osmium fixation (%)	^{192}Ir eluted (%) during fixation	^{191m}Ir* yield (%)	^{191}Os breakthrough (%/5 ml)
DARCO					
4 X 12	Lignite	99.6	36.4	32.4	9.3×10^{-3}
LI-100	Coal (low iron)	99.9	11.5	4.5	4.9×10^{-3}
H-85	Coal	99.8	11.7	4.2	1.3×10^{-2}
20 X 40	Lignite	99.9	6.5	18.8	3.7×10^{-3}
12 X 20LI	Lignite (low iron)	99.8	7.1	23.6	6.7×10^{-3}
Fischer	Coconut Shell	99.9	10.3	18.8	6.2×10^{-3}
Barneby-Cheney	Coconut	99.9	31.5	31.4	2.8×10^{-3}

* Each bolus consisted of a 5 ml volume.

glass wool. The top of the carbon bed is covered with a fine layer of glass wool and a specially designed Teflon "plunger" that fits snugly into the syringe barrel is inserted. The Teflon plunger has a hole drilled along the long axis and is fitted at the top with a tubing connector. In this manner, readily available syringes can be used for the generator body (Fig. 2).

Prior to loading, the column is washed with 20 ml of pH 2-0.9% NaCl prepared by addition of 20 ml of 0.5*M* HCl to 980 ml of physiological saline solution. The generator is loaded with the $^{191}Os(IV)$ solution with a syringe pump at a rate of about 0.25 ml/min and washed with 20 ml of pH 2-0.9% NaCl solution at the same flow rate. The system is then washed with 50 ml of

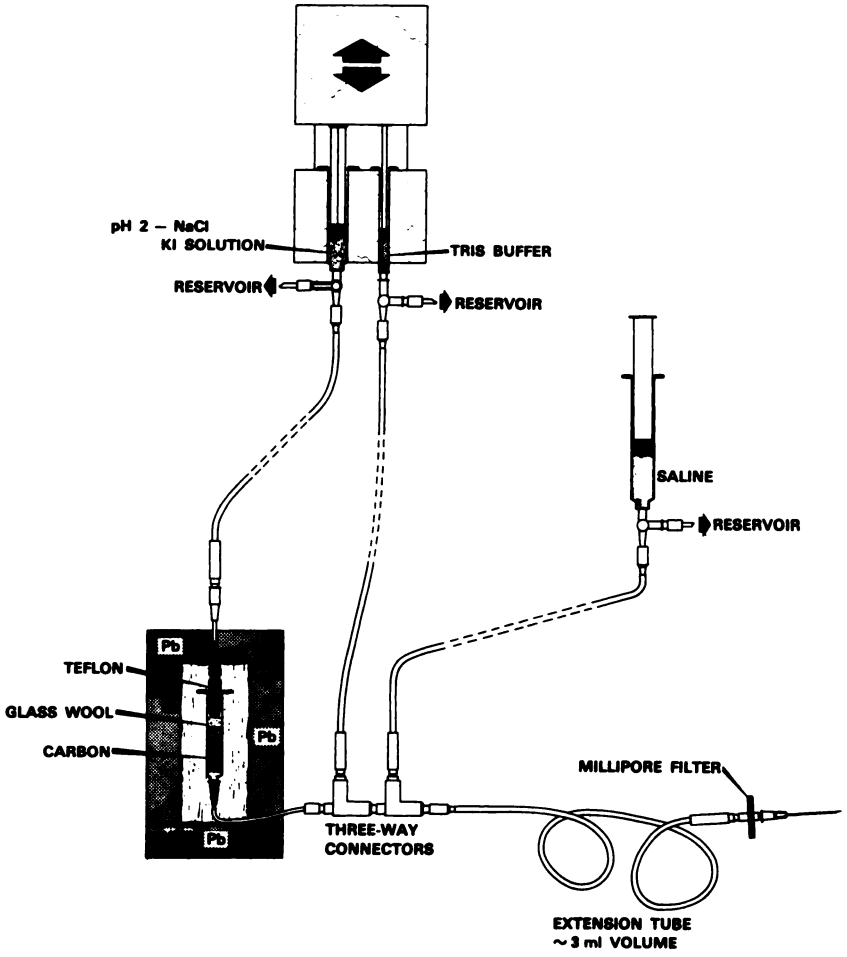

FIGURE 2
Schematic diagram of fabrication and eluting system for carbon-based prototype generator

eluting solution of composition pH 2-0.9% NaCl containing 0.250 g KI/l (0.025%) and is ready for use. For a typical generator system loaded with 700 mCi of ^{191}Os(IV) (specific activity = 200 mCi/mg), the ^{191m}Ir bolus is eluted with 2.5 ml of eluting solution. Neutralization of the acidic eluent is accomplished by the assembly shown in Fig. 2. A second syringe containing 0.4 ml of 0.13*M* Tris buffer acidified to pH 8.4 with HCl is emptied simultaneously with the elution syringe resulting in immediate neutralization of the generator eluent. The bolus is stored in a 3-ml extension tube and is injected as quickly as possible by means of physiological solution contained in the injection syringe. In the system illustrated, commercial two-way connectors (XKEM-001-04) have been used.§ Readily available intravenous extension tubing and arterial pressure tubing are used with this system. For shielding, standard ORNL 2-in. lead shipping pigs have been modified as shown in Fig. 2 to allow use of the pig as the shielded container. In this way the shipping pig can be used for shielding after receipt, and transfer of the generator column to a second shielded container is not necessary. The extension tubing is simply attached to the short lengths of tubing which are capped with Luer dead-end caps during shipment. A study of the automation of this system is underway.

Yield and Breakthrough Measurement

Because of the very short 4.96-sec half-life of ^{191m}Ir, special techniques described previously (*25*) must be used for determination of ^{191m}Ir yield. After elution of the generator, the ^{191m}Ir must be allowed to decay sufficiently to overcome large gross count loss resulting from the detector deadtime. The decay period, denoted as the waiting time, T_W, can be monitored accurately with a stop watch. Alternatively, one can use a digital timer to actuate the counting system after T_W sec. The use of a digital timer is very convenient, since T_W can vary depending on the levels of ^{191m}Ir eluted. After waiting T_W sec, the eluate is counted with a NaI(Tl) detector connected to a multi-channel analyzer under defined geometric conditions. Samples are counted for T_C sec, where T_C corresponds to at least eight times the half-life of the daughter nuclide (i.e., 40 sec). The energy and the intensity of the measured gamma-ray were 129.4 keV and 0.259, respectively. After the decay of the ^{191m}Ir, the samples are counted again for T_C sec to determine the contribution of the ^{191}Os to the number of counts previously measured (breakthrough). The levels of ^{192}Ir eluted in the bolus are also determined at this time.

The ^{191m}Ir activity, A (^{191m}Ir), in μCi at the end of the bolus elution was calculated by the relationship:

$$A(^{191m}\text{Ir}) = \frac{[N(^{191m}\text{Ir}) - N(^{191}\text{Os})]x\lambda}{\epsilon \times \gamma \times 3.7 \times 10^4 \times e^{-\lambda T_w}}, \quad (1)$$

where A (^{191m}Ir) = ^{191m}Ir activity in the sample at the end of elution (μCi);
N (^{191m}Ir) = gross number of counts of ^{191m}Ir measured for T_C sec;
N (^{191}Os) = net number of counts measured for T_C sec for ^{191}Os after decay of eluted ^{191m}Ir;
λ = decay constant of ^{191m}Ir (sec^{-1});
ϵ = efficiency of the counter at the energy of measurement under the defined geometrical conditions;
γ = intensity of the gamma-ray measured; and
T_w = waiting time before counting (sec).

The elution yield, Y(%), is given by the simple relationship:

$$Y(\%) = \frac{A(^{191m}\text{Ir}) \times 100}{A(^{191}\text{Os})}, \quad (2)$$

where A (^{191}Os) is the ^{191}Os activity in μCi on the column. The ^{191}Os activity in the samples is determined in the usual way and the ^{191}Os breakthrough is formulated as the ratio of the ^{191}Os activity in the eluate solution to the ^{191}Os activity on the column.

To measure the elution yield of a generator continuously eluted at a flow rate of, f (ml/min), 1 ml is sampled after the passage of the equilibrium activity bolus for T_S sec (T_S = 60/f) and counted in the same manner as for bolus. The ^{191m}Ir activity is calculated by Eq. (1). The elution yield is then given by the following equation:

$$Y(\%) = \frac{A(^{191m}\text{Ir}) \times 100}{A(^{191}\text{Os}) \times (1 - e^{-\lambda T_S})}. \quad (3)$$

ABSORBED DOSE ESTIMATES

Detailed distribution studies performed in female Fisher rats were used as the basis for the dose estimates. Animals were killed at various time intervals up to 8 days, with four time points in the first day. Eleven organs were studied, plus blood, urine, and feces. The animal % kg injected activity per g values were converted to % injected activity per organ values in the human. Values for total excretion were assumed to apply directly to humans. Values were analyzed using either linear or nonlinear least squares techniques to fit the retention data to either one- or two-compartment exponential retention functions, respectively. A one-compartment exponential ingrowth function was included in some cases. Organ residence times were calculated from these functions, and dose estimates were generated using the MIRD technique (*26*). The dynamic urinary bladder of Cloutier et al. (*27*) was used for activity

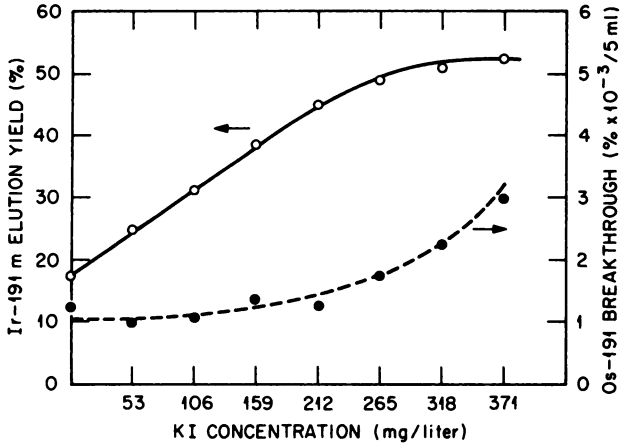

FIGURE 3
^{191m}Ir and ^{191}Os breakthrough as function of KI concentration

clearing through the urinary pathway. The GI tract model described in ICRP 30 (*28*) was used for material clearing through the GI. The excess cumulated activity correction (*29*) was used for activity in the remainder of the body.

RESULTS

The goal of the present study was to further evaluate the merits of activated carbon as an adsorbent for a new ^{191}Os/^{191m}Ir generator system. Osmium-191 in the form of hexachloroosmate (K_2OsCl_6, Os-IV) is more stable than Os(VIII), Os(VI) or Os(III) and was used to load the generators. The ^{191m}Ir yield and ^{191}Os breakthrough, determined as described earlier (*16–18*), were evaluated using several sources of activated carbon (lignite, coconut, wood, etc.). The results of these screening studies are summarized in Table 1. Seven different commercial carbon products were evaluated under the same conditions. These results suggested that Barneby-Cheney carbon was the best candidate for further study. Both yield and breakthrough varied in an unpredictable manner using carbon from different sources. Since the properties of the carbon products varied so much, the possibility that either specific functional group or trace element content was affecting the properties as a generator was investigated. Since activated carbon is known to contain oxygen-carbon functional groups (-COOH, -CH_2OH, -CHO, etc.), group modification by room temperature oxidation with HNO_3, $KMnO_4$, H_2O_2, HOCl, etc., was studied. These treatments had little effect. In addition, x-ray fluorescence analysis showed that yield and breakthrough could not be correlated with trace element content.

Thermal treatment and chemical analysis, however, indicated that the carbons contained varying amounts of KI and I_2. Because of proprietary considerations, manufacturers do not describe the production and activation methods for their carbon products. Thus, the presence of large amounts of KI and I_2 was unexpected and was detected by established methods. One source of coconut carbon (140-230 mesh) gave reasonably consistent results with ~35–40% yield and ~1×10^{-3}%/5 ml breakthrough and was used for further study and for the development of the prototype ^{191}Os/^{191m}Ir generator described below.

The ^{191m}Ir yield and ^{191}Os breakthrough were measured with increasing concentrations of KI in the pH 2 saline eluent (Fig. 3). These results demonstrate the importance of the presence of iodide ions in optimizing the ^{191m}Ir elution yields. Also, the addition of KI results in the elution of ^{191m}Ir as a discrete bolus (Fig. 4). Presumably, in the presence of iodide ions, hexachloroiridate ions are converted into hexaiodoiridate ions which are adsorbed less on activated carbon. Those considerations incited us to design a prototype generator using heat-treated carbon as adsorbent and eluted with 2.5 ml of a pH 2-0.9% NaCl solution containing 0.25 g KI/l. A typical elution profile is shown in Fig. 4. With a 2.5 ml volume, 85% of the equilibrium bolus activity is eluted with the activity effectively contained in 2.0 ml since the activity in the first 0.5 ml can be neglected. The elution characteristics of the prototype generator are summarized in Table 2. The ^{191m}Ir elution yield and the ^{191}Os breakthrough are independent of the time and a volume of 1,000 ml is allowed to pass through the generator without altering its properties.

This generator can also be eluted continuously. A low mean elution yield of 3.7% (range: 1.2 to 5.5% after 2 l of eluent) was measured at a flow rate of 12 ml/min with a mean ^{191}Os breakthrough of 2.0×10^{-5}%/ml (range: 1.7×10^{-5} to 2.9×10^{-5}%/ml) after 2 l. Due to its short half-life, the ^{191m}Ir grows very rapidly. Conse-

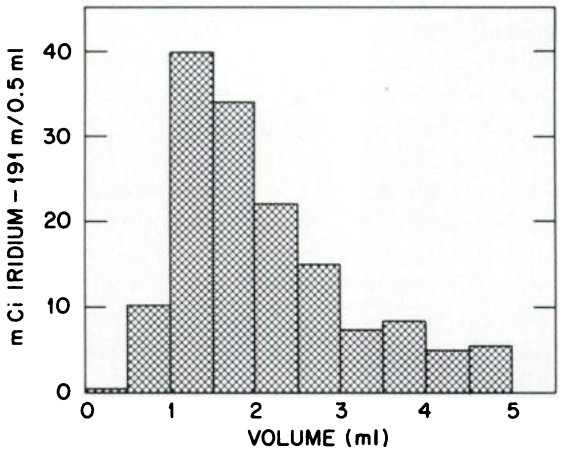

FIGURE 4
Typical elution profile of prototype ^{191}Os/^{191m}Ir generator system (^{191}Os activity of 700 mCi)

TABLE 2
Elution Characteristics of Prototype $^{191}Os/^{191m}Ir$ Generator No. 7 Prepared from Thermal-Treated 140-230 Mesh Barneby-Cheney Carbon Loaded with ^{191}OS (IV)

Bolus no.	Total* volume (ml) eluted	Elapsed time (days)	Values per 2 ml bolus ^{191m}Ir Yield (%)	^{191}Os breakthrough (%/2 ml)	^{192}Ir (μCi)
1	50	0	18	2.9×10^{-4}	0.7
50	175	1	17	2.5×10^{-4}	0.5
80	250	3	19	2.3×10^{-4}	0.4
110	325	8	18	2.3×10^{-4}	0.3
150	475	15	19	1.6×10^{-4}	0.2
280	750	20	21	1.7×10^{-4}	0.2
380	1,000	22	22	1.8×10^{-4}	0.3

* Each bolus consisted of a 2 ml volume eluted in approximately 1 sec.

TABLE 3
Estimates of Absorbed Doses from ^{191m}Ir, ^{191}Os and ^{192}Ir per Injected 2 ml Bolus (100 mCi ^{191m}Ir)*

Organ	mrad per 2 ml injection From ^{191m}Ir (mrad)	From ^{191}Os (mrad)	From ^{192}Ir (mrad)	Total (mrad)
Bladder	—	2.7	2.6	5.3
Brain	0.09	0.06	0.3	0.4
Small intestine	14.0	1.0	2.0	17.0
Heart walls	0.6	0.4	1.2	2.2
Kidneys	2.5	4.0	4.9	11.5
Liver	1.4	5.7	1.8	8.9
Lungs	0.8	0.4	1.3	2.5
Ovaries	1.4	0.8	2.2	4.4
Red marrow	1.5	0.9	2.0	4.5
Spleen	0.8	3.4	5.6	9.7
Testes	1.0	0.7	1.9	3.6
Thyroid	2.4	2.2	3.9	8.4
Total body	1.2	0.9	1.8	3.9

* 800 mCi ^{191}Os generator; ^{191}Os breakthrough 2.1×10^{-4}%/bolus; ^{192}Ir activity 0.35 μCi/bolus.

quently, even for such a low elution yield, the elution rate of ^{191m}Ir is as high as 1.3 mCi/sec at 12 ml/min for a 250 mCi ^{191}Os generator, which results in the injection of 6.5 mCi of ^{191m}Ir per injected ml. This activity is sufficient for many medical applications requiring continuous infusion. For the study described above, the measured ^{192}Ir activity was 0.020 μCi/ml. A volume of 2 l can pass through the generator before the ^{191}Os breakthrough increases to 5×10^{-5}%/ml.

DISCUSSION

The goal of the present studies was to develop a new $^{191}Os/^{191m}Ir$ radionuclide generator system which would provide ^{191m}Ir in consistently good yield with low ^{191}Os breakthrough. We have found that activated carbon is an excellent generator adsorbent and retains these properties for 2-3 wk. Consistently high yields of ^{191m}Ir are obtained over a prolonged period with multiple elutions, and breakthrough remains constant during this period. This simple generator design also does not require a scavenger column. The eluent is neutralized with a Tris buffer to give an isotonic solution at physiological pH ready for direct intravenous injection. The adsorption of ions on activated carbon has been described in many papers (*30-32*) where investigators have noted that osmium is adsorbed on activated carbon while iridium is not retained in 0.01 N NH_4Cl and in 0.01 N HCl solutions (*30*).

In the present work, >99.9% of the (^{191}Os) K_2OsCl_6 is bound to the activated carbon during the loading and washing procedures. Yields of 16-20% can be obtained in a 2.5 ml bolus elution volume. The void volume of a 200-400 mCi generator is 0.7-0.9 ml. The use of an automated system should allow the void volume to be discarded, making a smaller bolus of activity available for pediatric applications (*33,34*). Six prototype generators of this type have been used in clinical trials with no adverse effects detected in normal male volunteers after administration of 2.5 ml bolus injection using the system shown in Fig. 2. No radiolysis has been detected even after 3 wk for generators loaded with up to 1 Ci of ^{191}Os. Since the volumes of the eluent and buffer solution can be reduced proportionately, it should be possible to use this system for shunt evaluation in children which requires a small bolus of <1 ml. As an example, we have eluted this system with 1 ml of eluent simultaneously buffered with 0.16 ml of Tris buffer, with an elution yield of 10% ^{191m}Ir. Since ~20 mCi of ^{191m}Ir are usually used for radionuclide angiography of shunts in children (*10*), a 250 mCi generator would be expected to yield 25 mCi of ^{191m}Ir, more than sufficient for this measurement. In adults, ^{191m}Ir has been useful for the evaluation of left ventricular ejection fraction (LVEF) after administration of up to 100 mCi of ^{191m}Ir (*13*).

The radiation dosimetry values based on biodistribution in rats for eluates of our new prototype generator have been calculated, since the use of activated carbon with osmium in oxidation state (IV) are parameters which have not been previously studied. The absorbed dose estimates for several organs resulting from the injection of a 100 mCi ^{191m}Ir bolus are summarized in Table 3. The contributions of ^{191m}Ir, ^{191}Os, and ^{192}Ir are included.

FOOTNOTES

* W.S. Tyler Company, Mentor, Cleveland, OH.
† Barneby Cheney, Columbus, OH.
‡ Becton-Dickinson, Rutherford, NJ.
§ Millipore Corporation, Bedford, MA.

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