Ruthenium-97 DTPA: A New Radiopharmaceutical for Cisternography

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Ruthenium-97 DTPA (diethylenetriamine penta-acetic acid) was evaluated for its possible use as a cerebrospinal fluid imaging agent. Ru-97 has favorable physical properties that are highly suitable for imaging: decay by electron capture; gamma energy = 216 keV, 85%; $T_{1/2}$ = 2.9 days. Dogs were injected with 0.4 mCi Ru-97 DTPA or In-111 DTPA into the cisterna magna. The movement of the agents was monitored with a camera interfaced to a computer, or with a dual-probe system placed over the head and urinary bladder. In addition, blood and urine samples were collected at fixed intervals for 6 hr. High-quality images were obtained up to 48 hr after injection. The results show that the kinetics and excretion of Ru-97 DTPA are similar to those of In-111 DTPA. Radiation dose for identical activities is twice as high for In-111, in part because of greater abundance of the low-energy electron emission of In-111.

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The kinetics of albumin, inulin, and chelates in the cerebrospinal fluid (CSF) have been demonstrated to be similar (*1*), which makes each of these agents potentially useful for cisternography. Iodine-131 albumin and Tc-99m albumin have been used for cisternography (*2*), but side effects from these protein-containing agents have been described and substitution of inulin for albumin had been proposed (*3*). Chelated compounds (Yb-169 DTPA, Tc-99m DTPA, In-111 DTPA) have been used successfully for cisternography (*4–8*). The chelate is not toxic if used in small amounts (*4*). Although the biological half-life of intrathecally injected chelate is approximately 12 hr when normal reabsorption occurs, under certain pathological conditions or in cases of poor injections causing longer persistence of the tracer, Yb-169 DPTA may deliver a higher radiation dose due to its 32-day physical half-life (*6,8*).

On the other hand, the half-life of Tc-99m is too short (6.04 hr) for the evaluation of adult hydrocephalus, where 48- and 72-hr scans are needed (*9*). Today In-111 DTPA is the most commonly used agent for cisternography. Indium-111 has suitable physical characteristics ($T_{1/2}$ = 2.81 d, E = 173 and 247 keV) permitting prolonged studies as well as providing for adequate quality control (*8*). Ruthenium-97 appears to offer several advantages over In-111 as a label for DTPA, including lower radiation dose, especially at the cellular level due to lower abundance of low-energy electron emissions and better imaging qualities because of the predominantly monoenergetic photon. Ruthenium-97 decays by electron capture with no beta emission, has a half-life of 2.90 d, and a gamma energy of 216 keV in 85% abundance. The Ru-97 can be produced in cyclotrons by bombardment either of molybdenum with alpha particles or technetium-99 with protons. In high-energy cyclotrons and accelerators, Ru-97 can be produced by spallation reactions. Recently an efficient and economical production method (>100 mCi/day) of Ru-97 in the BLIP (Brookhaven Linac Isotope Producer) has been found feasible using the rhodium-103 (p,2p5n) Ru-97 reaction (*10*). Development of a number of useful radiopharmaceuticals labeled with Ru-97 has been investigated

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(*11*). This report presents data on the kinetics and dosimetry of Ru-97 DTPA for study of the dynamics and imaging of cerebrospinal fluid.

MATERIALS AND METHODS

Preliminary investigations were carried out using Ru-103 because of its longer half-life (39.6 d). Ruthenium-103 chloride* was obtained as a carrier-free solution in 3.5 *N* hydrochloric acid. Ruthenium-97 was prepared at the BLIP from proton spallation of high-purity (>99.9%) rhodium foils (*10*). Radioruthenium-labeled DTPA was prepared by dissolving 9 mg of $CaNa_2$ DTPA (diethylenetriamine penta-acetic acid) in 2 ml of 0.2 *N* NaOH and adding Ru-103 or Ru-97 chloride. The pH was adjusted to 3.5, after which the solution was placed in a boiling-water bath for 30 min with constant, gentle stirring by magnetic stirrer. It was then cooled to room temperature and the pH readjusted to 6.5. The solution was then passed through a 0.22-μm Millipore filter.

The quality control for Ru-103 DTPA and Ru-97 DTPA was carried out using a polyamide thin layer chromatography with 99.5% methanol as the developing solution, and also by electrophoresis in borate buffer (pH 8.0, 3MM paper, 1 hr development, 3 mA/strip).

Tissue distribution of Ru-103 DTPA was studied in mice and compared with that of In-111 DTPA. Hale-Stoner strain (Swiss Webster) female mice weighing ~25 g were injected i.v. with 2–3 μCi of either Ru-103 DTPA or In-111 DTPA and killed 30 min later. Organs were weighed and counted for Ru-103 and In-111 activity.

The following experimental setup was followed in six dogs each for the comparison of Ru-97 DTPA and In-111 DTPA.

Identical doses of In-111 DTPA and Ru-97 DTPA (0.4 mCi) were injected into the cisterna magna. The activity over the head and urinary bladder was monitored with 3-in. NaI(Tl) crystal probes. Blood was drawn at fixed intervals and the activity measured in a NaI(Tl) well scintillation counter. The bladder was catheterized and cumulative urine samples were obtained at 5 and 6 hr after injection. Scintiphotos of the head and lower abdomen were taken at different intervals after injection. Four dogs were killed 24 hr after injection, and tissue samples were taken after weighing the whole organs. Activity was measured in a NaI(Tl) well counter, with findings expressed as percent of injected dose/gram and per organ.

Radiation dosimetry for both In-111 DTPA and Ru-99 DTPA was determined by using the following data and assumptions:

1. Physical $T_{1/2}$ for Ru-97 and In-111 are 69.6 and 67.4 hr, respectively.
2. The removal of radiopharmaceuticals from CSF follows the relationships: Ru-97: $A = 0.83\, e^{-0.064t} + 0.17\, e^{-5.18t}$; In-111: $A = 0.90\, e^{-0.072t} + 0.10\, e^{-3.20t}$ (i.e., two-compartment curves with half-lives of ~10 and 0.2 hr).
3. Three compartments (CSF, blood, urinary bladder).
4. Cumulative time-activity in blood = 0.86 mCi-hr/mCi injected.
5. Average transit time through urinary bladder = 3 hr.
6. Dosimetry calculations were based on MIRD techniques (*12*), assuming that the values for absorbed fractions tabulated for the thyroid closely approximate those for studies where the source organ is the adjacent cerebral CSF. The limiting beta dose to spinal cord was calculated using the methods of Johnston et al. (*13*)† and Brookeman and Morin (*14*)—i.e., surface dose, with cord radius varying from 0.2 mm to its maximum value of ~8 mm.

Previous calculations for penetrating radiation have sometimes assumed that the source and target (CSF and spinal cord) were a right circular cylinder with a diameter of 1.6 cm and length of 60 cm (*13*). The absorbed fraction for penetrating radiation with this geometry was assumed to be 0.03 for I-131. A similar absorbed fraction (0.035) is found for the thyroid with I-131. Analogously, the absorbed fraction for the thyroid was found to be 0.055 for Ru-97 (thyroid = source and target). In these

TABLE 1. COMPARATIVE TISSUE DISTRIBUTION OF In-111 DTPA AND Ru-103 DTPA, INJECTED i.v. IN MICE*

	(t = 0.5 hr)			
	In-111 DTPA		Ru-103 DTPA	
Organ	%/g	%/organ	%/g	%/organ
Blood	0.44 ± 0.05	0.74 ± 0.08	0.79 ± 0.23	1.50 ± 0.45
Liver	0.22 ± 0.04	0.29 ± 0.05	0.61 ± 0.07	0.99 ± 0.11
Kidneys	1.59 ± 0.13	0.53 ± 0.03	2.48 ± 0.65	0.99 ± 0.23
GI	0.22 ± 0.06	0.85 ± 0.22	0.39 ± 0.10	1.50 ± 0.34
Excretion		92.98 ± 1.32		82.34 ± 7.18

* Each point represents mean ± s.d. for five mice.

TABLE 2. COMPARISON OF Ru-97 DTPA AND In-111 DTPA CONCENTRATIONS IN DOGS*

	(t = 24 hr)			
	Ru-97 DTPA		In-111 DTPA	
Organ	%/g	%/organ	%/g	%/organ
Brain	0.0650	6.5000	0.0650	4.8500
	(0.0460–0.0840)	(6.2400–6.7600)	(0.0580–0.0720)	(3.6700–6.0300)
CSF	0.210	—	0.2800	—
	(0.1600–0.2600)		(0.1500–0.4100)	
Bladder	0.0030	0.0300	0.0015	0.0106
	(0.0019–0.0041)	(0.0210–0.0390)	(0.0011–0.0019)	(0.0076–0.0136)
Blood	0.0007	0.8460	0.0002	0.2600
	(0.0006–0.0008)	(0.7440–0.9480)	(0.00018–0.00022)	(0.1500–0.3700)

* Each point represents mean and range for four dogs.

calculations, absorbed fractions for penetrating radiation tabulated for the thyroid were used in evaluating absorbed doses when the CSF/spinal cord was a source/target organ.† This model was used instead of the right circular cylinder, due in part to its general availability through its presence in the MIRD tables (*12*). The location of the thyroid in the body is fairly representative of the CSF, and in general it is perhaps no worse a model for the CSF than a 1.6- × 60-cm cylinder.

Integrated activities in CSF were higher than those reported by Brookeman and Morin (*14*), due in part to the fact that activity in CSF was measured at the site of injection and assumed to be 100% at time = 0. Further, removal of activity from CSF was significantly slower than that found for humans (*16*). Thus the spinal-cord dose should represent an upper limit, allowing mainly for a comparison of Ru-97 and In-111, rather than a definitive evaluation of absolute absorbed dose.

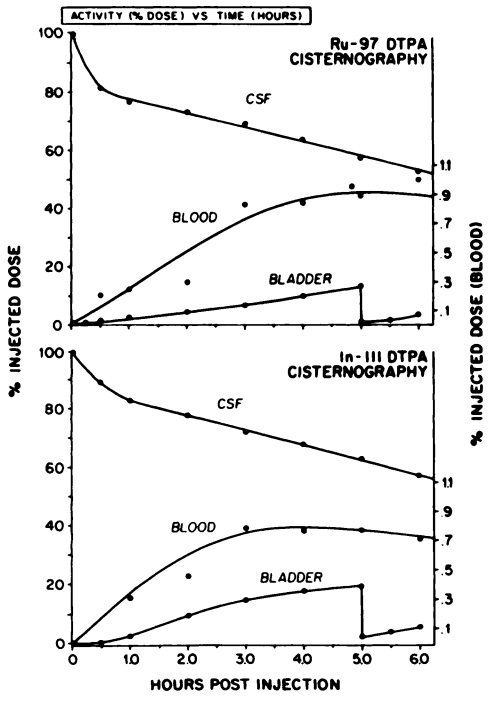

FIG. 1. Time-activity curves for CSF, blood, and urinary bladder after intracisternal injection of Ru-97 DTPA and In-111 DTPA. Each data point represent average for four dogs. Drop in bladder activity represents removal of urine accumulated between 0–5 hr, and thereafter buildup activity (5–6 hr) follows reclamping.

RESULTS

Upon electrophoresis on cellulose acetate in borate buffer (pH 8), the unbound ruthenium stays at the point of origin whereas ruthenium-DTPA moves toward the anode.

Thin layer chromatography (TLC) of In-111 DTPA was similar to that of Ru-97 DTPA, both compounds having $R_f = 1$. TLC and paper electrophoresis both indicated 97–99% chelation of the radiotracer.

The electrophoresis data, the chromatography on polyamide with methanol, and animal experiments demonstrated the formation of a Ru-DTPA complex.

Table 1 compares the tissue distributions of In-111 DTPA and Ru-103 DTPA in mice at 30 min after injection. The two tracers had comparable distribution patterns, except that the blood and liver levels were slightly higher with Ru-103 DPTA. The fact that more than 80% of Ru-103 DTPA is excreted by 0.5 hr is indicative of adequate chelation (*17*).

In dogs given the two compounds intrathecally, tissue concentrations of Ru-DTPA appeared slightly higher than those of In-111 DTPA, but the differences were not statistically significant (Table 2).

Figure 1 illustrates that the fast component of the disappearance curve of Ru-97 DTPA from the CSF is slightly steeper than for In-111 DTPA. The slow components have similar slopes. The blood curves, which represent the activity absorbed from the CSF, are similar, but Ru-97 DTPA persists in the circulation longer and its excretion is slightly slower than that of In-111 DTPA.

Table 3 shows the radiation deposited in selected or-

TABLE 3. RADIATION DOSIMETRY

Organ	Absorbed dose (rads/mCi) Ru-97	In-111
Spinal cord*	4.5–5.1	8.1–9.7
Blood	0.055	0.103
Bladder	0.693	1.350
Whole body	0.050	0.090
Ovaries	0.042	0.075
Testes	0.025	0.046

* Dose varies according to assumed cord diameter and depth from surface (Ref. *13*).

TABLE 4. FWHM FOR Ru-97 AND In-111

Nuclide	% window	Scattering material (in. paraffin)	FWHM
Ru-97	30	0	7.5
In-111	25	0	8.6
	25	3.6	15.3
	50	0	8.9
	50	3.6	17.1

gans after intracisternal injection of 1 mCi In-111 DTPA and 1 mCi Ru-97 DTPA. It can be seen that in all organs for which calculations were made, the radiation dose (per mCi injected) for In-111 DTPA is twice as high as that for Ru-97 DTPA. Images obtained with In-111 DTPA and Ru-97 DTPA are shown in Fig. 2. Note that the Ru-97 images (left side) are equally good or possibly better.

Table 4 indicates degradation in resolution observed with In-111 when 3.6 in. of scattering material is between source and collimator surface. Full width at half maximum increases to 17.1 mm when both In-111 peaks are used, as opposed to 15.3 mm with the high-energy peak alone. Resolution with Ru-97 alone was slightly better, due to the slightly reduced gamma energy.

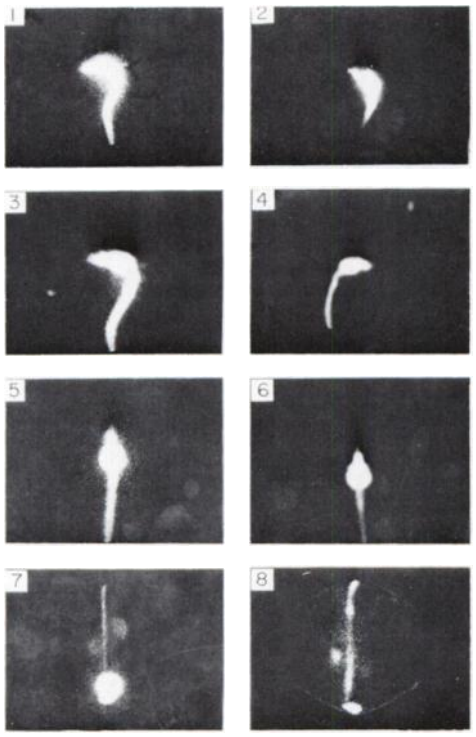

FIG. 2. Cisternograms in dogs injected intracisternally with 0.4 mCi each Ru-97 DTPA (Panels 1,3,5,7) and In-111 DTPA (Panels 2,4,6,8). Panels 1,2 are at 2 hr, 3,4 at 4 hr, and 5,6 at 48 hr (vertex view) after injection. Panels 7 and 8 are views of spine, kidneys, and bladder at 48 hr after injection.

DISCUSSION

The widespread use of transmission computerized tomography (TCT), which provides the clinician with good anatomical detail of the brain and its chambers, cannot provide sufficient information for the etiological classification of hydrocephalus. The cisternographic criteria necessary to differentiate various forms of hydrocephalus depend on observations obtained from delayed images (*17*). Of particular importance is the differentiation between normal-pressure hydrocephalus and dilated ventricles due to brain atrophy (*5*). In the former the resorption of CSF is slow, whereas in brain atrophy with dilated ventricles, CSF dynamics are normal.

Ru-97 DTPA can be used for these purposes because of its adequate physical properties and its biological behavior, which is similar to that of In-111 DTPA: It is absorbed from the CSF into the bloodstream and excreted rapidly in the urine. The slight differences between Ru-97 DTPA and In-111 DTPA are probably due to the longer persistence of Ru-97 in the blood, which may also explain the slightly higher tissue concentrations.

On a per-millicurie basis, Ru-97 delivers approximately half the absorbed dose to tissues, compared with In-111. This results from the larger abundance of gamma photons and associated internal conversion electrons emitted by In-111, which emits 0.896 and 0.940 gammas per disintegration with energies of 172 and 247 keV, respectively, whereas the primary emission of Ru-97 is a 216-keV photon, 85% of the time. For imaging with a single-energy photon, clearly Ru-97 would have an advantage. If both In-111 photons are used for imaging, the dose advantage (per photon) of Ru-97 is lost. The image quality for Ru-97 would then be expected to be better, however, since scattering of the 247-keV photon into the 172-keV energy region would degrade resolution for In-111. We therefore conclude that Ru-97 DTPA is superior to In-111 DTPA because of its lower radiation dose and better imaging properties.

FOOTNOTES

* Oak Ridge National Laboratories, Oak Ridge, TN.
† CSF volume assumed to be 120 ml for standard man (*15*).

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NOTICE

Please note that inside the front cover of this issue there is a loose insert of the corrected article entitled "Method for Optimizing Side Shielding in Positron-Emission Tomographs and for Comparing Detector Materials" by Stephen E. Derenzo.

Please replace the original pages (*J Nucl Med* 21: 971-977, 1980) with this article.