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November 9, 1984

'84 NOV 15 P2:13

Cassandra McDonald
Materials Licensing
Division of Fuel Cycle & Materials Safety
Office of Nuclear Materials Safety & Safeguards
U.S. Nuclear Regulatory Commission
Washington, D.C. 20555

RE: Methodist Hospital of Gary, Gary,Indiana 46402
License # 13-16558-01

Dear Ms. Cassandra McDonald:

This is in response to our telephone conversation yesterday concerning the request by our client, Methodist Hospital of Gary, Gary, Indiana, for exemption from 10 CFR 35.14 (b)(6) restrictions for radionuclide evaluation of ventriculo-atrial/ventriculo peritoneal shunts using Tc-99m pertechnetate. (This procedure is also referred to as CSF shunt evaluation).

We are providing references concerning the radiation dosimetry estimates for this study.

a. A. Everett James, M.D. in Pediatric Nuclear Medicine, Wm. B. Saunders Publishing, page 145.

   Radiation dose to cranial and cerebrospinal space tissue at site of injection: 0.27 rad/100 microcuries.

b. Valerie A. Brookeman, Journal of Nuclear Medicine, Volume 16, December 1975, pages 1175-1182, Dosimetry of Several DTPA Radiopharmaceuticals in Cisternography."

   Radiation dose for intrathecal administration of Tc-99m DTPA:

   0.2 rad/millicurie to spinal cord
   0.5 rad/millicurie to nerve roots

c. MIRD/Dose Estimate Report No. 8, Journal of Nuclear Medicine, Volume 17, January 1976, pages 74-77, "Summary of Current Radiation Dose Estimates to Normal Humans from Tc-99m as Sodium Pertechnetate."

We understand this was the remaining information necessary to complete the review of this request for exemption. We look forward to hearing of this regulations change and appreciate all your time and consideration to this project.

If there are any further questions, please contact Judy Budd at Methodist Hospital of Gary, (219) 886-4000 or Standard Nuclear Consultants, Ltd. at (312) 344-7308. Thank you.

Sincerely,

Stan W. Buhr

Stan Buhr

SB/jo

cc: Judy Budd, R.T.
Methodist Hospital of Gary

DOSIMETRY OF SEVERAL DTPA RADIOPHARMACEUTICALS IN CISTERNOGRAPHY

Valerie A. Brookeman and Richard L. Morin

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Previously published biologic distribution and clearance data for ^{169}Yb-DTPA in cisternography were utilized to obtain effective spinal segment clearance data for six other easily chelated radionuclides: ^{99m}Tc, ^{113m}In, ^{111}In, ^{67}Ga, ^{51}Cr, and ^{203}Pb. Absorbed radiation doses to the spinal cord and nerve roots were calculated for each radioactive DTPA compound, employing appropriate cylindrical geometry and reduction coefficients for the dose contributions from the electrons of each radionuclide. Doses are maximal at the surface and decrease rapidly with distance from the surface. The relative useful photon flux from each DTPA radiopharmaceutical for approximately the same average absorbed radiation dose to the spinal cord was determined. The results indicate that ^{111}In and ^{203}Pb should be considered as possible radionuclide tags for DTPA cisternographic imaging.

Radioactive diethylenetriamine pentaacetic acid (DTPA) offers several advantages over ^{131}I-IHSA for cisternography (*1–7*). We recently reported the distribution and clearance of ^{169}Yb-DTPA during cisternography and estimates of the absorbed radiation doses to the spinal cord and nerve roots (7). In this report we present absorbed radiation doses to the spinal cord and nerve roots during cisternography for six other radionuclides that also may be chelated. The doses for ^{99m}Tc, ^{113m}In, ^{111}In, ^{67}Ga, ^{51}Cr, and ^{203}Pb (*1,2,5*) are calculated from the biologic distribution and clearance data obtained with ^{169}Yb-DTPA.

MATERIALS AND METHODS

Since the method of obtaining effective spinal activity clearance data, corrected for body background, has been fully described previously (7), it will only be summarized in this report. Following intrathecal administration of 1 mCi ^{169}Yb-DTPA, spinal counts were obtained using a scintillation camera and computer system, at the routine cisternographic imaging times of approximately 2, 6, 9, 24, and 48 hr after injection, from nine patients, all of whom exhibited delayed flow. No normals were present in the group. Utilizing appropriate ^{169}Yb counting standards, the net activity in each segment at each time was obtained for six equal spinal segments, about 1.75 in.

Received Nov. 20, 1974; revision accepted June 20, 1975.

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TABLE 1. EASILY CHELATED RADIONUCLIDES

Radionuclide	Half-life (days)	Internal conversion and Auger electrons			
		Energies (keV)	Ranges in water (μm)	Net weighted mean energy (keV)	Range in water of mean energy (μm)
^{99m}Tc	0.25	0.4–142	0.02– 270	7	1.3
^{113m}In	0.07	0.7–392	0.04–1,230	98	130.0
^{111}In	2.81	0.6–246	0.03– 620	10	2.5
^{67}Ga	3.25	0.1–378	0.02–1,150	5	0.76
^{51}Cr	27.8	0.5–314	0.02– 890	2	0.14
^{203}Pb	2.17	3.0–666	0.33–2,560	21	9.0
^{169}Yb (7)	32.0	1.9–306	0.17– 830	13	5.0

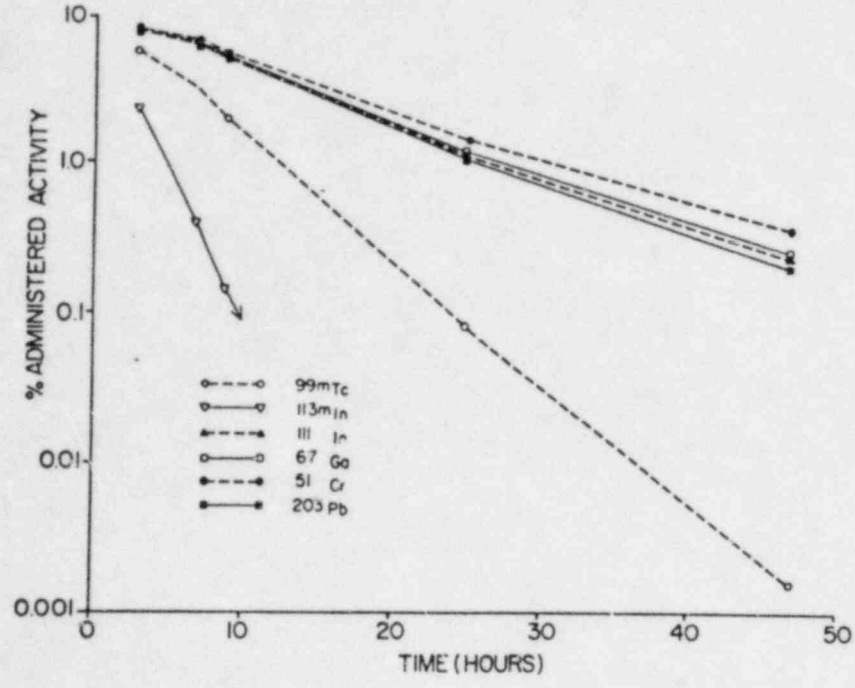

FIG. 1. Mean activity–time curves for radioactive DTPA in spinal Segment 4 (cord).

wide by 5 in. long, numbered sequentially from 1 to 6 in the caudal direction from the base of the skull to the tip of the coccyx. Segments 1–4 contain the spinal cord and Segments 5 and 6 contain nerve roots. The injection site is in Segment 5. The calculated percentages of administered activity represented the activity remaining as a result of both physical decay and biologic clearance of ^{169}Yb-DTPA.

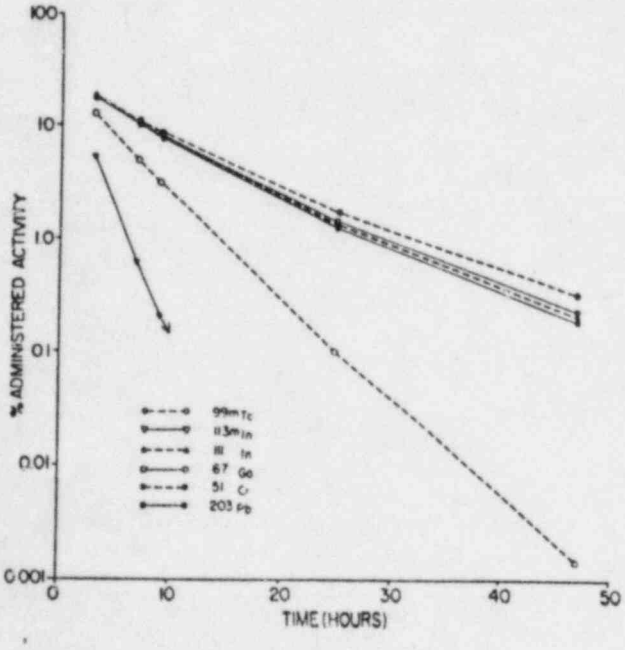

FIG. 2. Mean activity–time curves for radioactive DTPA in spinal Segment 5 (nerve roots).

The effective spinal segment clearance data for ^{169}Yb-DTPA (7) were converted to biologic clearance data by correcting for the physical decay of ^{169}Yb at each measurement time after injection. The biologic behavior of the DTPA chelate was assumed to be independent of the radionuclide tag (*4,8,9*). Hence, the resultant biologic clearance data were then corrected at each datum point for the physical decay of ^{99m}Tc, ^{113m}In, ^{111}In, ^{67}Ga, ^{51}Cr, and ^{203}Pb (Table 1) to yield effective spinal segment clearance data for each DTPA radiopharmaceutical.

RESULTS

Spinal segment activity. Curves of the mean percentage of administered activity for all patients as a function of time were derived for each spinal segment for each of the six DTPA radiopharmaceuticals. Figures 1 and 2 show these for spinal Segments 4 and 5 (the highest-activity segments containing spinal cord and nerve roots, respectively). All subsequent calculations and absorbed radiation dose estimates given for the spinal cord and nerve roots will be for spinal Segments 4 and 5.

Mean cumulated activities $\tilde{A}$ were calculated for complete elimination of each DTPA radiopharmaceutical by graphic integration of the mean activity–time curves (Figs. 1 and 2), assuming, more conservatively, that elimination after the last datum point occurs solely by physical decay $\tilde{A}(\infty)$ and, less conservatively, that the elimination rate obtained at the last datum point holds constant $\tilde{A}(t_{ef\ell})$ (7). Table 2 gives the cumulated activities for both elimination pathways for spinal cord and nerve roots for

TABLE 2. ESTIMATED MEAN CUMULATED ACTIVITY AND PHOTON DOSE TO SPINAL CORD AND NERVE ROOTS FOR INTRATHECAL ADMINISTRATION OF 1 mCi RADIOACTIVE DTPA

Radionuclide	Spinal cord			Nerve roots		
	$\tilde{A}(\infty)$ (μCi-hr)	$\tilde{A}(t_{eff})$ (μCi-hr)	Mean $\bar{D}_{ph}$ (rad)	$\tilde{A}(\infty)$ (μCi-hr)	$\tilde{A}(t_{eff})$ (μCi-hr)	Mean $\bar{D}_{ph}$ (rad)
^{99m}Tc	585	585	0.2*	1,107	1,107	0.5*
^{113m}In	143	143	0.1*	303	303	0.4*
^{111}In	1,453	1,310	2.5 ± 0.1	2,378	2,241	4.9 ± 0.1
^{67}Ga	1,518	1,329	1.4 ± 0.1	2,451	2,270	2.8 ± 0.1
^{51}Cr	4,829	1,449	0.7 ± 0.4	5,655	2,437	1.0 ± 0.4
^{203}Pb	1,354	1,271	1.7 ± 0.1	2,263	2,184	3.5 ± 0.1
^{169}Yb (?)	5,376	1,457	5.3 ± 3.0	6,160	2,451	7.9 ± 3.4

* Range of doses < 0.05 rad.

intrathecal administration of 1 mCi of the six DTPA radiopharmaceuticals. Since both methods of determining cumulated activity are extreme cases, the values therefore represent minimum-to-maximum ranges.

Dosimetry. The general dose equation and reciprocity principle (*10*) were employed as described previously (*7*). The spinal fluid volumes used in determining absorbed dose estimates for the spinal cord (Segment 4) and nerve roots (Segment 5) were 18 and 15.5 ml, respectively (*7*). Published values of the equilibrium dose constant (Δ_i) were utilized for ^{99m}Tc, ^{113m}In, ^{51}Cr (*11*), and ^{67}Ga (*12*). The Δ_i values for ^{111}In and ^{203}Pb were obtained through the courtesy of Dr. Robert H. Rohrer (*13*). Tabulated values of the absorbed fraction $\phi_i(r \leftarrow v)$ for photons of energy 14-keV and above were utilized, assuming a uniformly distributed source in a small 20-gm ellipsoid surrounded by a scattering medium (*14*). For photons of energy less than 14 keV and greater than 7.5 keV, $\phi_i(r \leftarrow v)$ values were derived for a right circular cylinder of radius 0.8 cm and height 11.7 cm (*7,15*). Photons of energy 7.5 keV and less were assigned a $\phi_i(r \leftarrow v)$ value of 1. The values of $\Sigma_i \Delta_i \phi_i(r \leftarrow v)$ for the photons of ^{99m}Tc, ^{113m}In, ^{111}In, ^{67}Ga, ^{51}Cr, and ^{203}Pb were 0.008, 0.018, 0.033, 0.018, 0.004, and 0.024 gm-rad/μCi-hr, respectively. The mean absorbed radiation doses from photons (D_{ph}) for 1 mCi of each DTPA radiopharmaceutical are given in Table 2 for the spinal cord and nerve roots.

The decay of each of the six radionuclides results in many low-energy internal-conversion and Auger electrons (Table 1), which are absorbed within very short distances from the surface of the spinal cord or nerve root. In order to determine accurately the mean absorbed radiation doses from electrons ($\bar{D}_e$) at different depths within the spinal cord and nerve roots, doses calculated from the general dose equation (with $\phi_i = 1$) must be multiplied by a dose reduction coefficient C, which takes into account the presence of a cylindrical source-free region (the cord or nerve root) (*7*). Values of C were computed (*16*) for the six radionuclides from the data of Berger (*17,18*) for cylinders of radii r = 0.5 cm (cord) and r = 0.05 cm (nerve root) and are plotted in Figs. 3 and 4, respectively, as a function of the depth within the cord or nerve root from the surface. The C values are maximal at the sur-

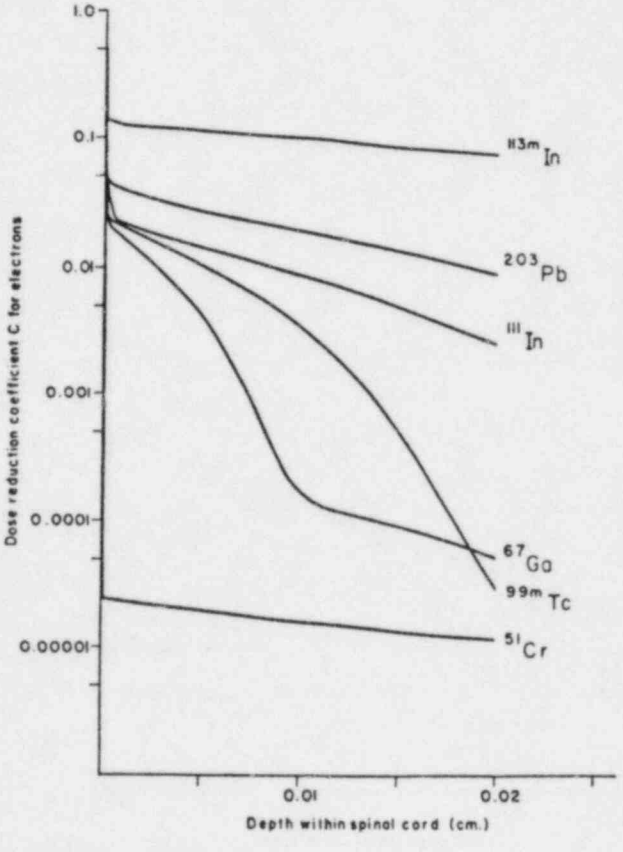

FIG. 3. Spinal cord dose reduction coefficients for electrons of six easily chelated radionuclides.

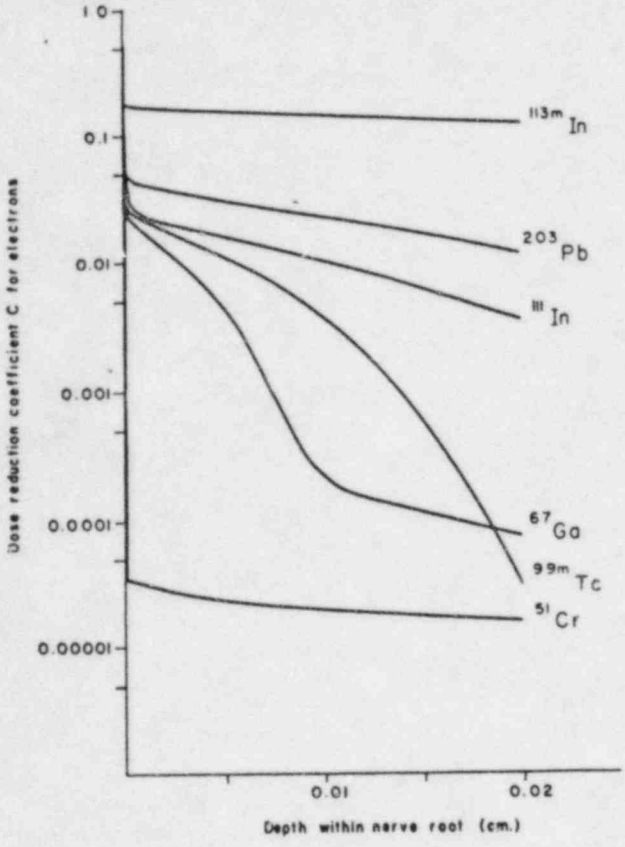

FIG. 4. Nerve root dose reduction coefficients for electrons of six easily chelated radionuclides.

face and decrease very rapidly with distance from the surface. At 0.01 cm [the thickness of the pia (*19*)] from the surface of the cord or nerve root, absorbed radiation doses from electrons range from 0.004% of the surface doses for ^{51}Cr to 26% for ^{113m}In.

The values of $\Sigma_i \Delta_i \phi_i(r \leftarrow v)$ for the electrons of ^{99m}Tc, ^{113m}In, ^{111}In, ^{67}Ga, ^{51}Cr, and ^{203}Pb were 0.036, 0.277, 0.077, 0.069, 0.008, and 0.116 gm-rad/μCi-hr, respectively. The appropriate value of C at each depth for each radionuclide was applied to the electron contributions ($\bar{D}_e$) to the calculated mean absorbed doses. The total mean absorbed radiation doses ($\bar{D}_{ph} + \bar{D}_e$) per millicurie of each DTPA radiopharmaceutical at various depths from the surfaces of the cord and nerve roots are given in Table 3. Doses are maximal at the surface, where $\bar{D}_e$ ranges from $1.04\bar{D}_{ph}$ for ^{51}Cr to $8\bar{D}_{ph}$ for ^{113m}In. At 0.0001 cm, $\bar{D}_e$ is negligible compared to $\bar{D}_{ph}$ for ^{51}Cr-DTPA and less than $0.3\bar{D}_{ph}$ for all the other radionuclides except ^{113m}In for which $\bar{D}_e$ is about $2.5\bar{D}_{ph}$. By 0.01 cm, $\bar{D}_e$ is only $0.02\bar{D}_{ph}$ or less for all the radionuclides except ^{203}Pb and ^{113m}In for which $\bar{D}_e$ is about $0.1\bar{D}_{ph}$ and $2\bar{D}_{ph}$, respectively.

DISCUSSION

The ranges given for the dose estimates in Tables 2 and 3 reflect the two methods of extrapolating the clearance data (Figs. 1 and 2) to infinity. There is, however, additional uncertainty in the dose estimates for the nerve roots due to the uncertainty of ±7.5 ml in the spinal fluid volume of 15.5 ml assigned to Segment 5 (*7*). Hence, all the dose estimates for the nerve roots may be additionally higher or lower by a factor of 1.9 or 0.7, respectively.

Since all patient data utilized in these absorbed radiation dose calculations showed slow cisternographic clearance (*7*), the cumulated activities and hence the dose estimates are higher than would be expected for cisternography in the normal individual.

Since the quoted thickness of the pia [0.01 cm (*19*)] only gives one order of magnitude, no precise delineation is made between "pia dose" and "cord dose." Hence the spinal cord doses in Table 3 are presented as a function of total depth from the surface including the thickness of the pia.

The absorbed radiation doses in Table 3 decrease rapidly with distance from the cord and nerve root surfaces and for all the radionuclide tags except ^{113m}In, reach their average values by 0.02 cm depth.

TABLE 3. MEAN TOTAL ABSORBED DOSES (RADS) TO SPINAL CORD AND NERVE ROOTS PER MILLICURIE OF INTRATHECALLY ADMINISTERED RADIOACTIVE DTPA

Radionuclide	Depth within spinal cord from surface (cm)					Depth within nerve root from surface (cm)				
	0.0	0.0001	0.001	0.01	0.02	0.0	0.0001	0.001	0.01	0.02
^{99m}Tc*	0.8	0.3	0.3	0.2	0.2	1.8	0.6	0.6	0.5	0.5
^{113m}In*	1.2	0.4	0.4	0.4	0.3	3.3	1.3	1.2	1.1	1.0
^{111}In	5.3 ± 0.3	2.7 ± 0.2	2.6 ± 0.1	2.5 ± 0.1	2.5 ± 0.1	10.6 ± 0.3	5.3 ± 0.2	5.1 ± 0.2	5.0 ± 0.1	4.9 ± 0.1
^{67}Ga	4.1 ± 0.3	1.5 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	8.2 ± 0.3	3.1 ± 0.1	3.0 ± 0.1	2.8 ± 0.1	2.8 ± 0.1
^{51}Cr	1.4 ± 0.7	0.7 ± 0.4	0.7 ± 0.4	0.7 ± 0.4	0.7 ± 0.4	2.1 ± 0.8	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.4
^{203}Pb	5.9 ± 0.2	2.2 ± 0.1	2.0 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	11.9 ± 0.2	4.5 ± 0.1	4.2 ± 0.1	3.9 ± 0.1	3.7 ± 0.1
^{169}Yb (7)	31.1 ± 17.9	8.8 ± 4.9	7.2 ± 4.2	5.8 ± 3.2	5.3 ± 3.1	46.6 ± 20.2	12.9 ± 5.6	10.9 ± 4.7	8.3 ± 3.6	7.9 ± 3.4

* Range of doses < 0.05 rad.

TABLE 4. COMPARATIVE USEFUL PHOTON FLUX FOR SAME APPROXIMATE RADIATION DOSE TO SPINAL CORD

Compound	Quantity administered intrathecally (mCi)	Useful gamma rays		Relative useful photon flux		
		Energy (keV)	Abundance per disintegration	At 0 hr	At 24 hr	At 48 hr
^{131}I-IHSA*	0.1	364	0.83 (11)	0.4	0.4	0.3
^{169}Yb-DTPA*	0.4	177 and 198	0.55 (13)	1.0	1.0	1.0
^{99m}Tc-DTPA	9.0	140	0.88 (11)	35	2.2	0.1
^{113m}In-DTPA	12.0	393	0.65 (11)	35	0.002	Negligible
^{111}In DTPA	0.9	172, 247	0.90, 0.94 (13)	3.6, 3.8	2.9, 3.0	2.3, 2.4
^{67}Ga-DTPA	1.5	91–388	0.02–0.4 (12)	0.1–2.6	0.08–2.0	0.05–1.5
^{51}Cr-DTPA	3.2	320	0.09 (11)	1.3	1.3	1.3
^{203}Pb-DTPA	1.2	279	0.81 (13)	4.3	3.2	2.4

* Utilizing results presented in Ref. 7.

These average values are solely caused by photons and persist throughout the cord and nerve roots. The doses from ^{113m}In-DTPA fall off most slowly with depth, as expected from the ^{113m}In electron dose reduction coefficients (Figs. 3 and 4). Technetium-99m gives the lowest radiation doses to the spinal cord and nerve roots, per millicurie of radioactive DTPA administered, followed by ^{113m}In and ^{51}Cr, ^{67}Ga, ^{111}In, and ^{203}Pb. The absorbed doses at the surface of the spinal cord and nerve roots per millicurie of tagged DTPA are greatest for ^{203}Pb (Table 3) but, as expected from the electron dose reduction coefficients (Figs. 3 and 4), these decrease more rapidly with depth than those for ^{111}In, which gives the largest doses per millicurie away from the surface.

The absorbed radiation dose estimates, however, do not give any indication of the relative usefulness for cisternography of each DTPA radiopharmaceutical in terms of useful photon flux and therefore image quality at various times after injection. Table 4 summarizes, for the six DTPA radionuclide tags under consideration and for ^{169}Yb and ^{131}I (*7*), the useful gamma rays and their abundance per disintegration. Also listed in Table 4 are the quantities of each radioactive DTPA compound and of ^{131}I-IHSA which, intrathecally administered, would result in about the same average dose to the spinal cord and about the same total radiation dose at 0.01 cm depth [the approximate pia thickness (*19*)]. Hence, utilizing this information and the physical decay of the radionuclides and assuming other things equal, the useful photon flux from the radiopharmaceuticals at 0, 24, and 48 hr after intrathecal administration of the quantities listed were determined (Table 4), relative to ^{169}Yb-DTPA. The values given for ^{131}I-IHSA at 24 and 48 hr assume that the rates of clearance of albumin and DTPA from the spinal subarachnoid space are equal. However, since the chelates appear to clear more rapidly from the cerebrospinal fluid circulation than albumin (*5,6*), the useful photon flux of ^{131}I-IHSA would be expected to increase with time following injection relative to the radioactive chelates, and hence the photon flux ratios of ^{131}I-IHSA compared to ^{169}Yb-DTPA at 24 and 48 hr will be slightly greater than given in Table 4.

Inspection of the photon flux ratios in Table 4 indicates that all the DTPA radiopharmaceuticals are superior to ^{131}I-IHSA. When useful cisternographic information can be obtained within 24 hr, ^{99m}Tc-DTPA offers considerable photon flux advantages as a cisternographic imaging agent. The longer physical half-lives (Table 1) of the radionuclides other than ^{113m}In and ^{99m}Tc result in photon fluxes which change much less drastically with time during the 48 hr after administration. Of the multiple-photon emissions from ^{67}Ga, the 93-keV gamma ray has the greatest abundance per disintegration: 0.4 (*12*). Lead-203-DTPA and ^{111}In-DTPA appear to be the best cisternographic agents of those considered. For the combined abundance (1.84) of both ^{111}In gamma rays, the photon flux from 0.9 mCi ^{111}In-DTPA is greater than that from 0.4 mCi ^{169}Yb-DTPA by a factor of 7.4–4.7 over a 48-hr period.

Other advantages in using radioactive chelates for cerebrospinal fluid scanning over ^{131}I-IHSA have been well documented (*1–7*). The choice of radionuclide tag for the chelate is based on the physical characteristics of each radionuclide and the radiation dose to spinal cord and nerve roots. Of the radionuclide-labeled chelates considered in this report, the following additional observations can be made. The higher-energy gamma rays of ^{111}In, ^{67}Ga, ^{51}Cr, and ^{203}Pb are not so flexible regarding collimation, while conversely

the lower-energy gamma rays of ^{169}Yb, ^{99m}Tc, ^{111}In, and ^{67}Ga are most suitable for use with the various new low-energy scintillation camera collimators commercially available. Short-lived ^{113m}In and ^{99m}Tc are not suitable for delayed studies or strict radiopharmaceutical quality control prior to administration. These disadvantages do not apply to ^{203}Pb, ^{111}In, and ^{67}Ga, with intermediate physical half-lives of 2–3 days (Table 1), or to ^{51}Cr and ^{169}Yb, with long physical half-lives, which additionally provide long radiopharmaceutical shelf-life.

ACKNOWLEDGMENT

The authors thank Lawrence T. Fitzgerald for writing the computer programs for determining the electron dose reduction coefficients. This work was presented at the 21st Annual Meeting of the Society of Nuclear Medicine, San Diego, Calif., June 11–14, 1974.

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mird / DOSE ESTIMATE REPORT NO. 8

SUMMARY OF CURRENT RADIATION DOSE ESTIMATES TO NORMAL HUMANS FROM ^{99m}Tc AS SODIUM PERTECHNETATE

January 1976

SUMMARY OF ESTIMATED ABSORBED DOSES TO NORMAL HUMANS FROM ^{99m}Tc AFTER A SINGLE INTRAVENOUS ADMINISTRATION OF LABELED SODIUM PERTECHNETATE*

Target organ	Absorbed dose (rads/mCi of ^{99m}Tc administered)	
	Resting population	Nonresting population
Bladder wall	0.053	0.085
Gastrointestinal tract:		
stomach (wall)	0.25	0.051
upper large intestine (wall)	0.068	0.12
lower large intestine (wall)	0.061	0.11
Ovaries	0.022	0.030
Red marrow	0.019	0.017
Testes	0.009	0.009
Thyroid	0.13	0.13
Total body†	0.014	0.011

* These dose estimates are for subjects not pretreated with blocking agents such as $NaClO_4$, $KClO_4$, or iodide.

† Technetium-99m is assumed to be distributed uniformly in the total body.

RADIOPHARMACEUTICAL

Technetium-99m-sodium pertechnetate as a radiopharmaceutical may be obtained as a sterile solution in isotonic sodium chloride or by elution from a sterile radionuclide generator. The *U.S. Pharmacopeia XIX* (*1*) specifies that the ^{99m}Tc present must be between 90 and 110% of the labeled quantity, of which 95% of the ^{99m}Tc must be present as pertechnetate. The allowable radionuclidic impurities, which will vary with the method of production, are also specified by the *Pharmacopeia* (*1*). For purposes of these dose calculations, the radionuclidic and radiochemical purity of the pharmaceutical are assumed to be 100%.

NUCLEAR DATA

Nuclear data for ^{99m}Tc are given in Table 1 (*2*). The decay of 1 mCi of ^{99m}Tc results in the production of approximately 3×10^{-9} mCi of ^{99}Tc (half-life 2.1×10^{5} year).

BIOLOGIC DATA

The human distribution and excretion functions for ^{99m}Tc-pertechnetate administered as sodium pertechnetate used in this report are based on a model developed by Hays and Berman (*3*). This model was constructed on the basis of data obtained by the authors, supplemented by published data (*4–8*), and subsequently modified by additional unpublished data provided by K. Lathrop. In developing the model, data on ^{99m}Tc activity in plasma, erythrocytes, saliva, stomach plus contents, intestine plus contents, urine, feces, and total body, derived from one or more of the above sources, were used. These data were obtained from subjects who had not been pretreated with blocking agents such as $NaClO_4$, $KClO_4$, or iodide. In analyzing the data in terms of the model it became apparent that they fell into two distinct groups possibly related to inactivity (resting) and to normal physical activity (nonresting) of the subjects. Hence, two sets of biologic parameters are derived, forming the bases for computing lower and upper radiation dose estimates.

A histogram of the distribution of ^{99m}Tc activity in the body as a function of time is presented in Fig. 1, and the biologic parameters are given in Table 2.

TABLE 1. NUCLEAR DATA*

Radionuclide	^{99m}Tc	
Physical half-life	6.03 hr	
Decay constant	0.1149 hr^{-1}	
Mode of decay	Isomeric transition	
Equilibrium dose constant for nonpenetrating radiation (gm-rad/μCi-hr)	0.0369	
Principal photons	E_i (MeV)	n_i
	0.0184†	0.077
	0.14†	0.879

* For complete compilation of nuclear data reader is referred to Ref. 2. Table lists only photons with mean yield per disintegration > 0.01; E_i is photon energy; n_i is mean number of photons per disintegration.

† Weighted mean energy of K x-rays.

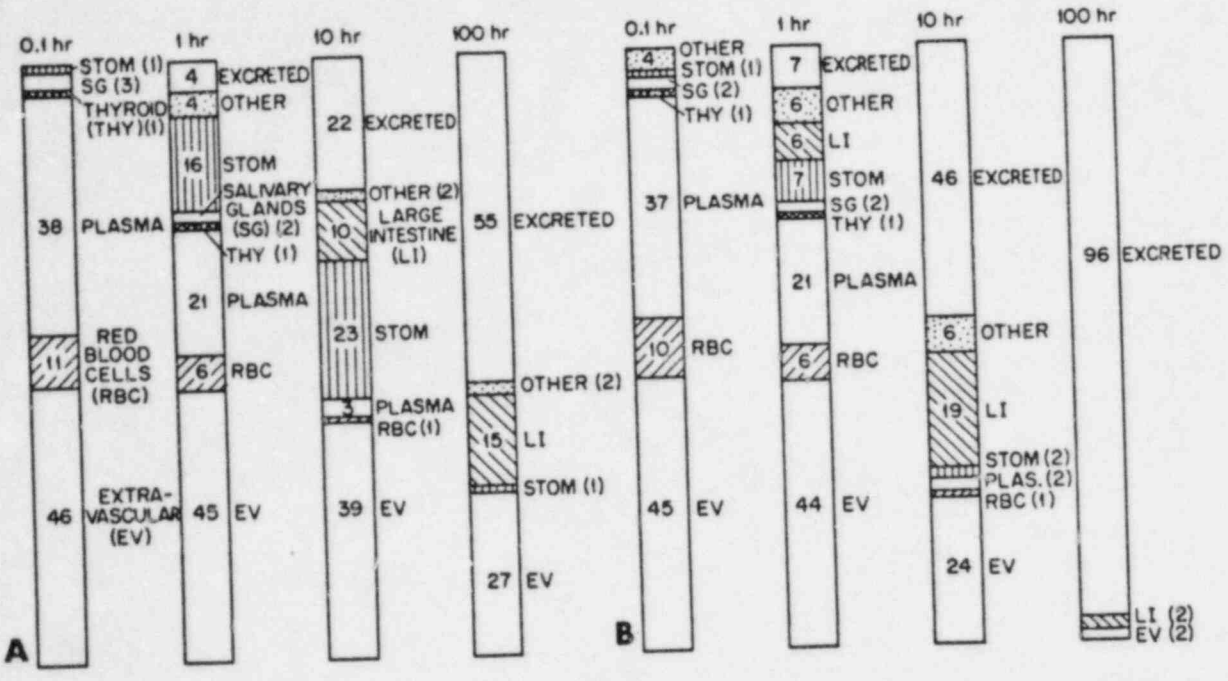

FIG. 1. Estimated percent of administered ^{99m}Tc in tissues at various times after intravenous administration of ^{99m}Tc-sodium pertechnetate. Corrected for radioactive decay. (A) Resting population; (B) nonresting population.

TABLE 2. BIOLOGIC PARAMETERS OF THE FRACTIONAL DISTRIBUTION FUNCTIONS $\alpha_{ih}(t)$ OF PERTECHNETATE FROM A SINGLE INTRAVENOUS ADMINISTRATION OF SODIUM PERTECHNETATE*

$$\alpha_{ih}(t) = \sum_j \alpha_{hj} e^{-\lambda_j t} = \alpha_{h1} e^{-\lambda_1 t} + \alpha_{h2} e^{-\lambda_2 t} + \alpha_{h3} e^{-\lambda_3 t} + \alpha_{h4} e^{-\lambda_4 t} + \alpha_{h5} e^{-\lambda_5 t}$$

Source organs	α_{h1}	α_{h2}	α_{h3}	α_{h4}	α_{h5}
Resting population	$\lambda_1 = 7.92$ hr^{-1}	$\lambda_2 = 0.630$ hr^{-1}	$\lambda_3 = 0.0702$ hr^{-1}	$\lambda_4 = 0.00396$ hr^{-1}	
Extravascular	−0.0739	0.0962	——	0.402	——
Large intestine	——	0.0107	−0.231	0.220	——
Plasma	0.093	0.301	0.0497	0.00582	——
Red blood cells	0.026	0.0860	0.0142	0.00132	——
Salivary glands	——	0.0300	0.00633	0.000546	——
Stomach	0.0345	−0.477	0.424	0.0191	——
Thyroid	−0.0199	0.0165	0.00307	0.000268	——
Total body†	——	0.0661	0.259	0.675	——
Nonresting population	$\lambda_1 = 7.98$ hr^{-1}	$\lambda_2 = 4.82$ hr^{-1}	$\lambda_3 = 0.553$ hr^{-1}	$\lambda_4 = 0.115$ hr^{-1}	$\lambda_5 = 0.0246$ hr^{-1}
Extravascular	−0.058	——	0.0199	0.268	0.194
Large intestine	−0.049	0.103	−0.266	−0.051	0.263
Plasma	0.124	——	0.259	0.060	0.0049
Red blood cells	0.036	——	0.074	0.017	0.0014
Salivary glands	−0.035	——	0.0270	0.0077	0.00057
Stomach	0.132	−0.214	0.0128	0.0656	0.0037
Thyroid	−0.0189	——	0.0149	0.0037	0.000285
Total body†	——	——	——	0.518	0.482

* The activity in the source region r_h at time t after administration of the radionuclide of activity A_0 is given by $A_h(t) = q_h(t)e^{-\lambda t}$, where $q_h(t) = A_0 \sum_j \alpha_{hj} e^{-\lambda_j t}$, α_{hj} is the initial value of the j^{th} exponential component of that fraction of the pertechnetate administered as sodium pertechnetate that appears in source region r_h, λ_j is the biologic disappearance constant of the j^{th} exponential component, and λ is the physical decay constant of the radionuclide. The cumulated activity in source region r_h over an infinite period is given by $\tilde{A}_h(0,\infty) = A_0 \sum_j \alpha_{hj}/(\lambda_j + \lambda)$.

† Values for total body include all tissues.

ABSORBED-DOSE ESTIMATES

The values of cumulated activity for the labeled pertechnetate located extravascularly, in plasma and in the red cells, were computed using the data in Table 2. The absorbed fractions for these source regions were assumed to be equal to those for sources uniformly distributed in the total body.

The activity contained in the large intestine was assumed to be uniformly distributed with respect to weight between the contents of the upper and lower large intestines. The above was an approximation since the fraction of the administered activity and its residence time in the intestinal wall were unknown. The dose to the intestinal wall was calculated on the assumption that the contents of the intestine were irradiating the wall.

The activity contained in the stomach was distributed between the contents of the stomach and the lumen of the gastric glands. The exact distribution between the two regions was unknown. For the purpose of these dose calculations, all of the activity was assumed to be located in the contents of the stomach.

To calculate the cumulated activity for the bladder contents, $\tilde{A}_{BLADC}$, the bladder was assumed to fill at a rate of 62.5 ml/hr and to empty completely five times daily at regular intervals of 4.8 hr (*9*). A maximum value of $\tilde{A}_{BLADC}$ was calculated by assuming that the bladder was empty at the time sodium pertechnetate was administered. The rate constant for plasma-to-urine transport of pertechnetate is 0.228 hr^{-1} for the resting population and 0.402 hr^{-1} for the nonresting population. The details for computing $\tilde{A}_{BLADC}$ are available from the MIRD Committee. The average dose to the bladder wall was computed using the method described by Snyder et al (*10,11*).

The salivary glands were used as source organs because of their high uptake of ^{99m}Tc. To obtain the necessary absorbed fractions for the salivary glands as a source organ, which are not yet available in the heterogeneous phantom (*12*), the absorbed fractions for the thyroid were used since the locations and sizes of these organs are similar. To calculate the dose to the thyroid from the activity in the salivary glands, only the absorbed fractions for penetrating radiations were used. It was assumed that the activity in the salivary glands was located in the thyroid. This approximation will result in an overestimate of the dose.

The masses of the target organs are given in Table 3.

The absorbed fractions used for the dose estimate calculations in this report were obtained from special Monte Carlo computer calculations, using the complete energy spectrum of penetrating and nonpenetrating radiation emitted by ^{99m}Tc, instead of from the interpolated values of absorbed fractions published in *MIRD Pamphlet No. 5* (*12*). The heterogeneous phantom (*13*) used for these calculations is a modification of that described in *MIRD Pamphlet No. 5* and more nearly simulates man.

The dose from the ^{99}Tc associated with ^{99m}Tc has been neglected since these doses are five orders of magnitude less than the dose from ^{99m}Tc.

TABLE 3. MASS OF TARGET ORGANS (13)

Target organ	Mass (gm)
Bladder wall	45
Gastrointestinal tract:	
stomach—wall	150
upper large intestine	
wall	209
contents	220
lower large intestine	
wall	160
contents	137
Ovaries	8.3
Red marrow	1,500
Testes	37
Thyroid	19.6
Total body	69,880

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ACKNOWLEDGMENTS

The work upon which this publication is based was performed pursuant to Contract No. FDA 223-74-6044 with the Public Health Service, Food and Drug Administration, Department of Health, Education, and Welfare.

TASK GROUP

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1.0 N hydrochloric acid in water; five sterile syringes (labeled "A"), each containing 1.9 mg sodium thiosulfate anhydrous in 1.1 ml aqueous solution; five sterile syringes (labeled "B"), each containing 5.3 mg gelatin in 2.1 ml aqueous buffer solution containing 177 mg sodium acetate anhydrous.

kit contents

5 STERILE REACTION VIALS, each containing 0.5 ml 1.0 N hydrochloric acid in water.

5 STERILE SYRINGES, (labeled "A"), each containing 1.9 mg sodium thiosulfate anhydrous in 1.1 ml aqueous solution.

5 STERILE SYRINGES, (labeled "B"), each containing 5.3 mg gelatin in 2.1 ml aqueous buffer solution containing 177 mg sodium acetate anhydrous.

10 PRESSURE-SENSITIVE LABELS for final Technetium Tc 99m Sulfur Colloid Injection preparation.

1 PACKAGE INSERT.

storage

Store kit at room temperature; refrigeration not required.

preparation

The following directions must be carefully followed for optimum preparation of the Technetium Tc 99m Sulfur Colloid Injection.

1. Affix finished drug label to reaction vial and lead shield with fitted cover then place vial in the lead shield.
2. Aseptically inject 0.1-5.0 ml of sterile Sodium Pertechnetate Tc 99m, up to 400 millicuries which must contain less than 10 micrograms of aluminum, into a shielded reaction vial. Relieve the excess pressure in the vial by withdrawing an equal volume of air. Mix the solution.
3. Assemble the thiosulfate syringe (labeled "A" in black print.)and inject the contents into the reaction vial with gentle agitation. Relieve the excess pressure by withdrawing an equal volume of air and remove the needle.
4. Remove reaction vial with tongs from vial shield and immediately immerse into a shielded vigorously boiling water bath, deep enough to cover the entire liquid contents of the vial. Keep the vial in the water bath for 5 minutes plus or minus 30 seconds.
5. During heating step, assemble buffer syringe cartridge (labeled "B" in red print.)
6. Remove vial from water bath, place in lead shield, and vent using a 10 cc syringe with a 20 gauge needle.
7. Immediately inject contents of syringe B into reaction vial.
8. Remove venting syringe, place fitted cover on lead shield and shake gently for a few seconds.
9. Cool to room temperature (note: solution may be cooled rapidly in a shielded ice bath if so desired) before use. Maintain adequate shielding of the radioactive colloid preparation. Do not use the preparation after six hours from the time of formulation. The preparation contains no bacteriostatic preservative.
10. Prior to removal of patient dose or patient injection, gently shake preparation to assure homogenous suspension.

Note: It is recommended that with proper shielding and equipment, the final formulation be tested for radiochemical purity (percent Technetium Tc 99m binding) and each patient dose be visually inspected for foreign matter. If the radiochemical purity is not adequate or foreign matter is observed in the patient dose, it is recommended that the patient dose be discarded.

It is recommended that with proper shielding the reaction vial be visually inspected for foreign matter. If foreign matter is observed, the prepared solution should not be used.

† Lead Shield available, Catalog No. 5708.

*Assembly of Syringes:

1. Carefully screw the plunger rod into the rubber plunger. (Do not press on plunger.)
2. Holding the syringe in an upright position (plunger rod down), with a slight twisting motion remove the gray rubber tip guard.
3. If needle is not affixed, place the disposable needle on the upright syringe by pressing firmly with a slight twisting motion.

disposal

The residual materials may be discarded in ordinary trash provided the vials and syringes read background with an appropriate low range survey meter. All identifying labels should be destroyed before discarding.

This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Sec. 35.14 and Sec. 35.100 Group III of 10 CFR Part 35 or under equivalent licenses of Agreement States.

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TECHNETIUM 99m

TSC

TECHNETIUM Tc 99m SULFUR COLLOID KIT

For ordering or technical information, contact manufacturer:

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August, 1981 6 Printed in U.S.A. L313-9

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TECHNETIUM 99m

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TECHNETIUM Tc 99m SULFUR COLLOID KIT

DIAGNOSTIC—FOR INTRAVENOUS USE

description

Each kit contains sufficient material to prepare (5) five formulations. Each formulation consists of a reaction vial containing 0.5 ml 1.0 N hydrochloric acid, and two syringes, one containing a 1.1 ml aqueous solution of 1.9 mg sodium thiosulfate anhydrous and the other containing 5.3 mg gelatin in 2.1 ml of an aqueous buffer solution containing 177 mg sodium acetate. All components are sterile and pyrogen-free. When a solution of sterile and pyrogen-free Sodium Pertechnetate Tc 99m in isotonic saline is mixed with these components, following the instructions provided with the kit, Technetium Tc 99m Sulfur Colloid Injection is formed. The product so derived is intended for intravenous injection. The precise structure of Technetium Tc 99m Sulfur Colloid Injection is not known at this time.

physical characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours[1]. Photons that are useful for detection and imaging studies are listed in Table I.

table I. principal radiation emission data

radiation	mean %/disintegration	mean energy (keV)
Gamma-2	88.97	140.5

[1] Martin, M.J., Evaluated Nuclear Structure Data File, Nuclear Data Project, Oak Ridge National Laboratory, 1977.

5

1

external radiation

The specific gamma ray constant for Technetium Tc 99m is 0.8 R/millicurie-hour at 1 cm. The first half-value thickness of lead (Pb) for Technetium Tc 99m is 0.2 mm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table II. For example, the use of 2.5 mm of Pb will decrease the external radiation exposure by a factor of 1,000.

table II. radiation attenuation by lead (Pb) shielding

shield thickness (Pb) mm	coefficient of attenuation
0.2	0.5
0.8	10^{-1}
1.6	10^{-2}
2.5	10^{-3}
3.3	10^{-4}

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals relative to the time of calibration are shown in Table III.

table III. physical decay chart:
Tc 99m, half-life 6.02 hours

hours	fraction remaining	hours	fraction remaining
0*	1.000	7	.447
1	.891	8	.398
2	.794	9	.355
3	.708	10	.316
4	.631	11	.282
5	.562	12	.251
6	.501		

*Calibration Time (Time of Preparation).

clinical pharmacology

Following intravenous administration, Technetium Tc 99m Sulfur Colloid Injection is rapidly cleared by the reticuloendothelial system from the blood with a nominal clearance half-life of approximately 2½ minutes. Uptake of the radioactive colloid by organs of the reticuloendothelial system is dependent upon both their relative blood flow rates and the functional capacity of the phagocytic cells. In the average patient 80 to 90% of the injected colloidal particles are phagocytized by the Kupffer cells of the liver, 5 to 10% by the spleen and the balance by the bone marrow.

indications and usage

Technetium Tc 99m Sulfur Colloid Injection is used as an agent for imaging areas of functioning reticuloendothelial cells in the liver, spleen, and bone marrow.

contraindications

None known.

warnings

The contents of the two syringes, one syringe containing the sodium thiosulfate solution and the second syringe containing the appropriate buffer solution, are intended ***only*** for use in the preparation of the Technetium Tc 99m Sulfur Colloid Injection and ***are not to be directly administered to the patient.***

The contents of the kit are not radioactive. However, after the Sodium Pertechnetate Tc 99m is added, adequate shielding of the final preparation must be maintained.

precautions

The components of the kit are sterile and pyrogen-free. It is essential that the user follows the directions carefully and adheres to strict aseptic procedures during preparation of the colloid.

The stability of the colloidal preparation may be decreased in the presence of polyvalent cations, thus resulting in the agglomeration of the individual colloidal particles. These larger particles are likely to be trapped by the pulmonary capillary bed following intravenous injection.

It is recommended that Sodium Pertechnetate Tc 99m solutions containing more than 10 micrograms/ml of aluminum ion not be used for formulation of the Technetium Tc 99m Sulfur Colloid Injection. The Sodium Pertechnetate Tc 99m solution must also be free of any traces of oxidizing agents such as peroxides and hypochlorites.

Technetium Tc 99m Sulfur Colloid Injection is physically unstable and as such the particles will settle with time. Failure to agitate the vial adequately before use may result in non-uniform distribution of radioactivity.

It is also recommended that because of the increasing probability of agglomeration with aging, a batch of Technetium Tc 99m Sulfur Colloid Injection not be used after **six** hours from the time of formulation.

The preparation contains no bacteriostatic preservative.

Pregnancy Category C. Animal reproduction studies have not been conducted with Technetium Tc 99m Sulfur Colloid. It is also not known whether Technetium Tc 99m Sulfur Colloid can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Technetium Tc 99m Sulfur Colloid should be given to a pregnant woman only if clearly needed.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Safety and effectiveness in children have not been established.

Technetium Tc 99m Sulfur Colloid Injection, as well as other radioactive drugs, must be handled with care and appropriate safety measures should be used to minimize external radiation exposure to clinical personnel. Also, care should be taken to minimize radiation exposure to patients, consistent with proper patient management.

Do not use the preparation after six hours from time of formulation.

adverse reactions

Hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving sulfur colloid preparations.

One death and several cases of lung and soft tissue uptake other than RES have been reported in the association with the use of Technetium Tc 99m Sulfur Colloid Injection.

drug abuse and dependence

There is no report of any drug abuse or dependence with this diagnostic agent.

overdosage

Increased radiation exposure would be expected if an overdosage of the diagnostic agent occurred.

dosage and administration

The suggested intravenous dose range used in the average patient (70 kg) is 1 to 8 millicuries of Technetium Tc 99m Sulfur Colloid Injection.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

radiation dosimetry

The estimated absorbed radiation doses[12] to an average patient (70 kg), or to patients with diffuse parenchymal liver disease from an intravenous injection of a maximum dose of eight millicuries of Technetium Tc 99m Sulfur Colloid Injection are shown in Table IV.

table IV. radiation doses

absorbed radiation doses (rads) 8 millicuries Tc 99m

tissue	normal liver	diffuse parenchymal disease	
		early-intermediate	intermediate advanced
Liver	2.7	1.7	1.2
Spleen	1.7	2.2	3.4
Bone Marrow	0.77	0.36	0.63
Testes	0.0088	0.017	0.026
Ovaries	0.045	0.065	0.096
Whole body	0.15	0.15	0.14

[12] Modified from: Summary of Current Radiation Dose Estimates to Humans with Various Liver Conditions from ^{99m}Tc-Sulfur Colloid. MIRD Dose Estimate Report No. 3. *J. Nucl. Med.*, 16, No. 1, 108A-B (1975).

Target	Hospital Technician Preparation of Drug* (milli rem/400mCi)	Administering Drug* (milli rem/8mCi)
Extremity Dose	23. milli rem	2. milli rem
Whole Body Dose	1. milli rem	0.1 milli rem

*Using shielded vial and syringe

how supplied

The TECHNETIUM 99m SULFUR COLLOID KIT is supplied as a sterile pyrogen-free kit consisting of: five reaction vials, each containing 0.5 ml