Absorbed Radiation Dose to Humans from Technetium-99m-Teboroxime

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Tissue distribution data obtained in nine normal volunteers were used to estimate the radiation dose to humans after intravenous administration of ^{99m}Tc-teboroxime (Cardiotec). Organ uptake as percent of injected dose was measured using quantitative SPECT. Non-linear regression analysis was performed on the organ time-activity data using SYSTAT® software. Cumulative activities in these organs were determined by calculating the area under the respective curves after accounting for the physical decay of the radionuclide. The absorbed dose to individual organs was estimated using the MIRDOSE 2 program. The gallbladder and the upper large intestine (ULI) are the target organs and will receive respectively 26.5 and 33.2 μGy/MBq (98 and 123 mrad/mCi) ^{99m}Tc-teboroxime under the assumption that the gallbladder empties every 6 hr. The dose to the gallbladder decreases at shorter emptying intervals; with intervals of 3, 4, and 5 hr, the respective doses to the gallbladder are 18.2, 21.0 and 23.7 μGy/MBq (67.4, 77.8, and 87.9 mrad/mCi) ^{99m}Tc-teboroxime. However, the dose to ULI remains almost constant at 123 mrad/mCi and will be the limiting factor.

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Teboroxime (Cardiotec) is a neutral, lipophilic ^{99m}Tc-labeled agent for myocardial perfusion imaging. Its high myocardial extraction and rapid clearance characteristics qualify this agent for use in clinical imaging with an advantage to rapidly complete the rest and exercise perfusion studies (*1,2*). The clinical efficacy of this agent using a kit formulation has been clearly established (*3–5*). Teboroxime has high myocardial extraction and fast washout such that rest and stress images can be obtained in less than 90 min. We have reported estimations of the human absorbed radiation dose following intravenous administration of ^{99m}Tc-teboroxime based on biodistribution data in rats (*6*). We now report the human absorbed radiation dose estimations following intravenous administration of ^{99m}Tc-teboroxime based on biodistribution in humans obtained in Phase I clinical trials. The estimations are made using the MIRDOSE 2 program, which uses the ICRP 30 gastrointestinal (GI) model to estimate the cumulative activities in the gut segments based on the fractional dose entering the small intestine (SI) (*7–9*).

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METHODS

Data Collection

Human biodistribution data were obtained in a total of nine (four in Group A and five in Group B) normal volunteers (Phase I clinicals). Each subject received a single intravenous injection of 11–15 mCi ^{99m}Tc-teboroxime at rest.

In Group A subjects, serial anterior planar images of the chest were obtained for the first 90 min postinjection (p.i.), and time-activity curves were constructed to determine the myocardial uptake and clearance of ^{99m}Tc-teboroxime. From 2–4 hr p.i., planar anterior images of the heart, lungs, liver, gallbladder, spleen, brain, thyroid, abdomen, and urinary bladder were acquired to qualitatively examine the biodistribution. Blood clearance was determined from serial samples drawn from 30 sec to 4 hr p.i. Cumulative urine samples were collected from 0 to 4 and 4 to 24 hr after drug administration.

Group B subjects were imaged using both planar and SPECT procedures to obtain quantitative organ uptake data. Serial planar images of the myocardium, lungs, liver, bladder, brain and thyroid were acquired over the first 90 min p.i. and at 1-hr intervals up to 6 hr. Eight-minute SPECT images of heart-lungs, liver-spleen, and brain-thyroid were obtained between 5 and 365 min p.i. Blood and urine samples were collected as described for Group A patients. Regions of interest (ROIs) were drawn over the myocardium, lungs, and other desired organs. In general, the entire organ was included in the ROI unless precluded by overlap. The total number of counts in each ROI, the time period over which the counts were collected and the number of pixels in each region were recorded and the counts per pixel were calculated.

Planar anterior images of Group B subjects were used to define the shape of the time-activity curves for each organ, and quantitation was achieved by relating planar counts to SPECT data. SPECT data were corrected for attenuation and scatter using the method of Jaszczak, Greer and Coleman (*10*). Counts were then decay-corrected and transformed into percent injected dose (%ID). Blood and urine samples were quantitated by comparing the sample radioactivity with a standard of 0.02 %ID.

Data Analysis

The SPECT data of the five Group B subjects consists of 7–11 acquisitions from each subject obtained from 5 to 365 min after injection. The data were treated as a single set by obtaining the average value of all the acquisitions at a given time point and using the number of acquisitions (patients imaged at that time point) as the weighting factor for that data point. For example,

in analyzing the heart data, we used a weighting factor (W_T) of 5 for the 2-hr data point as it represents an average of five acquisitions from five patients and a W_T of 4 for the 3-hr data point, as there were only four acquisitions at this time point. This was done because there was only a small number of data points and individual acquisitions were not obtained at exactly the same times. Non-linear regression analysis was performed on the organ time-average activity data using the program SYSTAT® assuming that the uptake in liver, lungs, heart and brain was instantaneous. Liver and brain time-activity (T/A) data were fitted to a mono-exponential function; and heart and lung T/A data were fitted to a bi-exponential function. The following functions best describe

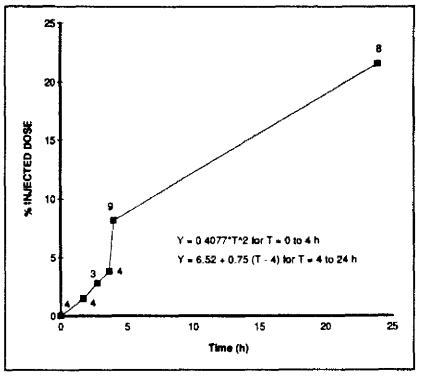

FIGURE 2. The urine activity (%ID) as a function of time (h). The smoothed line represents the two fit functions in the intervals 0–4 hr and 4–24 hr. The numbers close to the data points represent the weighting factor for obtaining the average value.

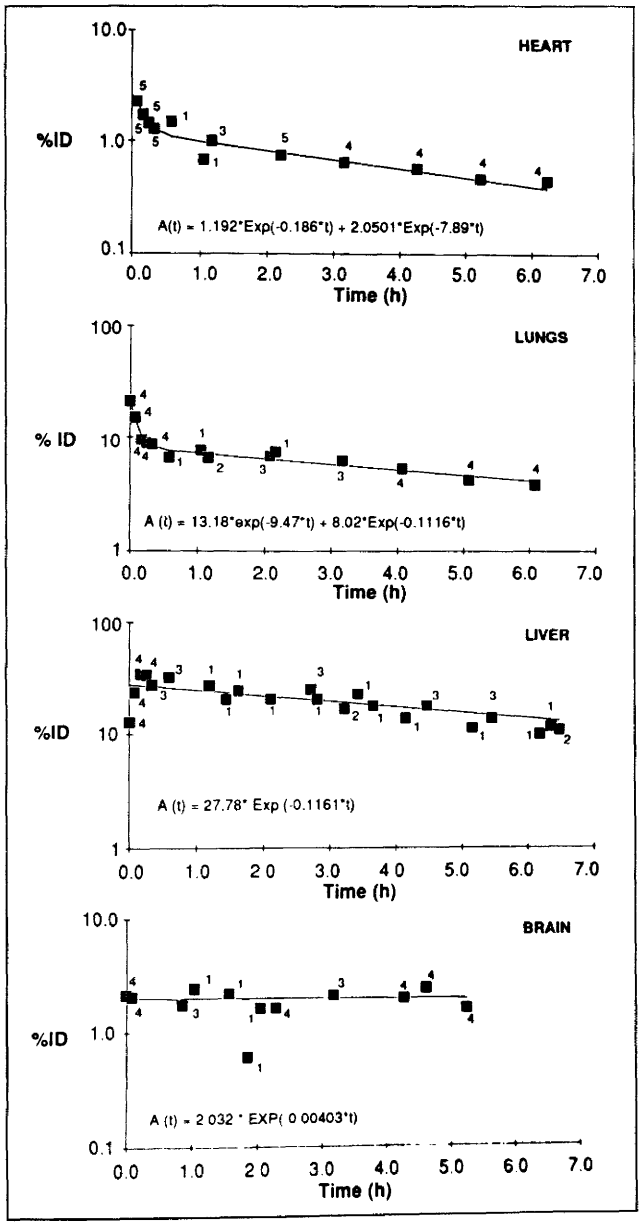

FIGURE 1. The graphs show tissue average activity (%ID) as a function of time for heart, lungs, liver, and brain along with the respective fit functions. The weighting factor for each data point is shown next to it (for details see text). The fit functions that best describe the data are given under each curve.

the data sets and were shown to be statistically the most appropriate:

$$A_{Liver}(t)(\%ID) = 27.78 \cdot e^{-0.1161t}$$

$$A_{Brain}(t)(\%)ID = 2.03 \cdot e^{-0.0040t}$$

$$A_{Lungs}(t)(\%ID) = 13.18 \cdot e^{-9.47t} + 8.02 \cdot e^{-0.1116t}$$

$$A_{Heart}(t)(\%ID) = 1.19 \cdot e^{-0.1860t} + 2.05 \cdot e^{-7.890t}.$$

The average data as a function of time, the weighting factor of each data point and the best fit function for each of these organs are shown in Figure 1.

The activity data in the feces were not collected, but were determined by assuming that the rate of ingrowth of fecal activity is dependent on liver clearance rate and is expressed by:

$$A_{Feces}(t)(\%ID) = 27.8 \cdot (1 - e^{-0.1161t}).$$

Urinary excretion data were collected in all nine subjects. During the first 4 hr, an average of 8.2% of the injected dose was excreted in urine, and from 4 to 24 hr 12.9% was found in the urine. Total urinary excretion averaged 21.6%.

Bladder activity was determined from SPECT data up to approximately 4 hr p.i., and the measured activity in the urine that was voided between 0 and 4 hr and between 4 and 24 hr p.i. Urinary excretion data were fitted to:

$$A_{Urine}(t)(\%ID) = 0.4077*t^2 \text{ for } t = 0 \text{ to } 4 \text{ hr}$$

and

$$A_{Urine}(t)(\%ID) = 6.52 + 0.75(t - 4) \text{for } t = 4 \text{ to } 24 \text{ hr}.$$

Urine activity (%ID) as a function of time and the best fit functions in the intervals 0–4 hr and 4–24 hr are shown in Figure 2.

Total body activity is assumed to be equal to 100 − (%activity excreted in feces + %activity excreted in urine). Thus:

$$A_{Total\ Body}(t)(\%ID) = 100 - (A_{Feces}(t) + A_{Urine}(t)).$$

Total body activity as a function of time estimated from the above equation is shown in Table 1. These data are best described by:

$$A_{Total\ Body}(t)(\%ID) = 12.66 \cdot e^{-0.3646t} + 87.34 \cdot e^{-0.0213t}.$$

A graph of the estimated total body activity as a function of time, along the fit function, is shown in Figure 3.

The activity in the gallbladder is determined with the assumption that one-third of the activity that leaves the liver is diverted

TABLE 1
Total Body Activity (%ID) of Teboroxime in Humans

Time (hr)	Feces	Urine	Total Body
1	3.05	0.41	96.55
2	5.76	1.63	92.61
3	8.17	3.67	88.16
4	10.32	6.52	83.16
5	12.23	7.27	80.49
6	13.94	8.02	78.04
7	15.46	8.77	75.77
8	16.81	9.52	73.67
9	18.01	10.27	71.72
10	19.08	11.02	69.90
11	20.03	11.77	68.19
12	20.88	12.52	66.59
13	21.64	13.27	65.09
14	22.31	14.02	63.66
15	22.91	14.77	62.32
16	23.45	15.52	61.03
17	23.92	16.27	59.81
18	24.34	17.02	58.63
19	24.72	17.77	57.51
20	25.06	18.52	56.42
21	25.35	19.27	55.37
22	25.62	20.02	54.36
23	25.86	20.77	53.37
24	26.07	21.52	52.41

through the gallbladder. Thus, the growth in gallbladder activity is represented by:

$$A_{Gallbladder}(t)(\%ID) = (27.8/3)\cdot(1 - e^{-0.1161t})$$

$$= 9.26\cdot(1 - e^{-0.1161t}).$$

The radioactivity in the gallbladder as a function of time for an emptying time of 6 hr is shown in Figure 4.

Calculation of Cumulative Activities and Biological Half-life

The MIRDOSE 2 program was used to obtain the absorbed dose estimations. The program requires the input of the residence times of the radiotracer in source organs and the biological half-time of the tracer in the bladder. Residence time is defined as the cumulative activity in μCi-h/μCi (3.6×10^3 MBq s/MBq) injected dose.

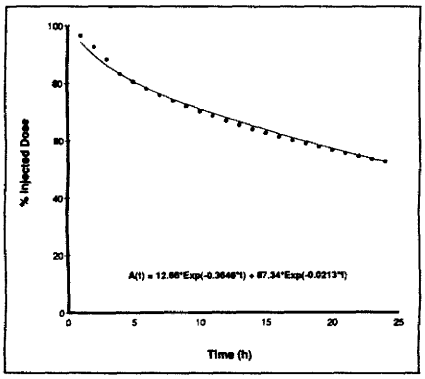

FIGURE 3. The estimated total body activity as a function of time and the fit function. The total body activity is assumed to be equal to 100 (%activity excreted in feces + %activity excreted in urine). The estimates are given in Table 1.

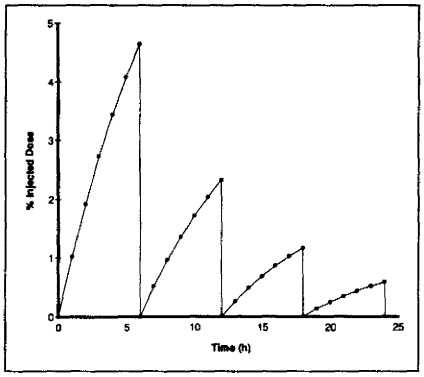

FIGURE 4. Time course of activity in the gallbladder for an emptying interval of 6 hr. It was assumed that one-third of the activity that leaves the liver is eliminated through the gallbladder.

Cumulative activities in the source organs are calculated based on the following procedures and assumptions:

1. Cumulative activities in the source organs were obtained by integration of the respective fit functions, from t = 0 to t = infinity, after accounting for the physical decay of the radionuclide.
2. Uptake in liver, lungs, heart and brain was assumed to be instantaneous.
3. It was assumed that two-thirds of the activity leaving the liver goes directly into the small intestine and the remaining one-third is stored in the gallbladder prior to excretion.
4. The gallbladder empties into the small intestine every 6 hr. Other intervals of 3, 4 and 5 hr were also considered.
5. It was assumed that all the activity in the liver is excreted in the feces and the ingrowth of fecal activity is dependent upon the liver clearance rate.
6 Urine activity up to 4 hr p.i. was obtained from the bladder activity data in Group B subjects and the 0–4 hr urine activity. The total fraction of injected activity excreted in urine was determined as the average of cumulative urine radioactivity from Subjects 1–9 out to 24 hr.
7. A 2-hr urination interval was assumed. When radioactivity is administered to a patient, in order to reduce the radiation dose, invariably the patient is advised to void more frequently. Moreover, a 2-hr urination interval is commonly used in dosimetry estimations.
8. Whole-body activity was determined by assuming that all activity not accounted for by fecal and urinary excretion was generally distributed.

The area under the curve for liver, lungs, brain, heart and total body was obtained by computing the activity (%ID) –time (h) integrals between t = 0 and t = infinity of the respective functions after taking into account the physical decay of ^{99m}Tc. The area under the curve, in μCi-h, of an organ corresponds to the cumulative activity in that organ for a 100-μCi injected dose.

An example of organ cumulative activity calculation is shown below:

$$A_{Total\ Body}\ (Cumulative) = 12.66 \int_0^\infty e^{-0.3646t}\cdot e^{-0.1155t}$$

$$+ 87.34 \int_0^\infty e^{-0.0213t}\cdot e^{-0.1155t}dt = 666\ \mu Ci\text{-h}/100\ \mu Ci\ ID.$$

Radiation dose to all target organs from remaining body activity can be calculated either by applying a correction to the cumulative activity in total body to account for the cumulative activities

in the other source organs or a correction to the S values so that a value of S for the target organ from the remainder of the body is obtained. Coffey and Watson showed that both methods give the same results (*11*). We have applied the correction to the cumulative activity of total body to obtain the cumulative activity in the remaining body.

Thus, the value for cumulative activity of "Remainder" to be used in MIRDOSE2 is the "Total Body" cumulative activity minus that of other identified source organs, except the excretory organs. The cumulative activity of the "Remainder" equals:

$$\text{Remainder (Cumulative)} = \text{Cumulative } (A_{\text{Total Body}} - (A_{\text{Liver}} + A_{\text{Heart}} + A_{\text{Lungs}} + A_{\text{Brain}} + A_{\text{Gallbladder}})$$

$$= 474.7\ \mu\text{Ci-h}/100\ \mu\text{Ci ID.}$$

The cumulative activity for gallbladder was determined using the output of the liver as the input to the same dynamic kinetic model of the urinary bladder for gallbladder emptying times of 3, 4, 5 and 6 hr.

The program computes the residence times for small intestine, upper large intestine, lower large intestine based on the ICRP 30 GI model (*9*). However, it requires the input for the fractional dose that enters into the small intestine. This is calculated to be 0.232, which is 5/6 of the fraction (0.278) that entered the liver. This is arrived at based on assumptions 2 and 3 and realizing that one-third of the liver activity (that entered the gallbladder) enters into the small intestine 6 hr later; by then the activity has decayed by 50% (of 1/3).

In order to obtain the biological half-time of the tracer in the bladder, a function describing the retention of activity in the body associated with the urinary pathway was defined. It is assumed that this artificial compartment has 72.2% of the total activity at t = 0 (100 − the total fecal excretion) and values after that correspond to 72.2% minus the cumulative urinary excretion (%ID) as a function of time. Activity associated with the urinary pathway as a function of time was best described by the following monoexponential function:

$$A_{\text{Bladder}}(t) = 71.56 \cdot e^{-0.0145t}.$$

The biological half-time of the tracer in the bladder is calculated, from this bladder time-activity function, as 47.8 hr (0.693/0.0145).

RESULTS AND CONCLUSIONS

The absorbed radiation dose in μGy/MBq ^{99m}Tc-teboroxime injected dose for gallbladder emptying intervals of 3, 4, 5 and 6 hr are given in Table 3. The mean absorbed radiation dose to a target organ from the activity in itself and other source organs is the sum of the products of cumulative activities in the source organ and the respective "S" factors between the source and target organs. The S factors do not change with the activity in the organs; they depend on the radiation characteristics of the isotope and the size, nature, and distance between the source and target organs. Thus, the variation we expect from variations in the gallbladder emptying interval will be proportional to the cumulative activities in the source organs that contribute to the dose. Liver, total body and gallbladder are respectively the primary, secondary and tertiary contributors to the gallbladder dose based upon size. Moreover, the cumulative activity in the gallbladder, as shown in Table 2, is highest for the 6-hr emptying interval, and for other emptying intervals of 3, 4, 5 hr the cumulative activities are smaller than that for the 6-hr interval. Thus, the dose to the gallbladder increases with longer emptying intervals; with intervals of 3, 4, 5 and 6 hr, the respective doses to the gallbladder are 18.2, 21.0, 23.8 and 26.4 μGy/MBq ^{99m}Tc-teboroxime injected. The dose estimates in cGy/37 MBq, cGy/1110 MBq and cGy/1850 MBq for gallbladder emptying intervals of 6 hr are shown in Table 4.

Using the weighting factors, W_T, for the various organs given in ICRP Pub. 26 and the dose estimates for gallblad-

TABLE 2
Calculated Cumulative Activities of ^{99m}Tc-Teboroxime in Source Organs

Organ	Cumulative activity (μCi-h/μCi or 3.6 × 10^3 MBq s/MBq)
Liver	1.20
Lungs	0.37
Heart	0.42
Brain	0.17
Remainder	4.75
Gallbladder* (6 hr interval)	0.20

* The values for other emptying intervals of 3, 4, 5 hr, respectively, are 0.12, 0.15 and 0.18 μCi-h/μCi or in units of 3.6 × 10^3 MBq s/MBq.

TABLE 3
Comparison of Radiation Dose Estimates of ^{99m}Tc-Teboroxime at Different Gallbladder Emptying Intervals*

Organ	Absorbed dose (μGy/MBq) 3 hr	4 hr	5 hr	6 hr
Brain	3.41	3.41	3.41	3.41
Gallbladder	18.22	21.03	23.76	26.41
SI	18.19	18.22	18.27	18.30
ULI	32.98	32.98	32.98	33.25
LLI	23.57	23.57	23.57	23.57
Heart wall	5.43	5.43	5.46	5.46
Kidneys	5.38	5.41	5.43	5.46
Liver	16.57	16.65	16.70	16.76
Lungs	7.57	7.57	7.57	7.57
Spleen	4.00	4.03	4.03	4.03
Thyroid	2.89	2.89	2.89	2.89
Ovaries	9.73	9.73	9.73	9.76
Testes	2.81	2.81	2.81	2.81
Red marrow	4.46	4.46	4.46	4.49
Urinary bladder	7.38	7.41	7.41	7.41
Total body	4.46	4.46	4.49	4.49

* 2-hr urinary bladder voiding interval.

TABLE 4
Absorbed Radiation Dose Estimates of ^{99m}Tc-Teboroxime (Gallbladder Emptying Interval of Six Hours)*

Organ	Absorbed Dose rads/mCi or cGy/37 MBq	rads/30 mCi or cGy/1110 MBq	rads/50 mCi or cGy/1850 MBq
Brain	0.013	0.34	0.57
Gallbladder	0.098	2.94	4.90
SI	0.068	2.04	3.40
ULI	0.123	3.69	6.15
LLI	0.087	2.61	4.35
Heart wall	0.020	0.60	1.00
Kidneys	0.020	0.60	1.00
Liver	0.062	1.86	3.10
Lungs	0.028	0.84	1.40
Spleen	0.015	0.45	0.75
Thyroid	0.011	0.33	0.55
Ovaries	0.036	1.08	1.80
Testes	0.010	0.30	0.50
Red marrow	0.017	0.51	0.85
Urinary bladder	0.027	0.81	1.35
Total body	0.017	0.51	0.85

* 2-urinary bladder voiding interval.

TABLE 5
Comparison of Human Radiation Dose Estimations from ^{99m}Tc-Teboroxime Based on Human Biodistribution and Rat Biodistribution Data

Organ	Absorbed dose (cGy/37 MBq or rads/mCi) Human data*	Rat data†
Brain	0.013	0.003
Gallbladder	0.098	
SI	0.067	0.170
ULI	0.123	0.160‡
LLI	0.087	
Heart wall	0.020	0.013
Kidneys	0.020	0.049
Liver	0.062	0.057
Lungs	0.028	0.010
Spleen	0.015	0.019
Thyroid	0.011	0.012
Ovaries	0.036	0.051
Testes	0.010	0.029
Red marrow	0.017	0.025
Urinary bladder	0.027	0.018
Total body	0.017	0.015

* Gallbladder emptying interval of 6 hr.
† From ref. 5.
‡ Dose to the entire large intestine.

der emptying interval of 6 hr, the effective dose equivalent, H_E, for ^{99m}Tc-teboroxime was estimated to be 12.8 μSv/MBq (*12*).

The human radiation dose estimations based on human biodistribution data and rat biodistribution data are compared in Table 5. Except for the dose to the small intestine, for which the rat distribution data yields a significantly higher dose, both sets of data give similar radiation doses. This may be explained by the fact that rat does not have a gallbladder and thus all the activity leaving the liver goes directly into the small intestine. The combined dose of 0.166 cGy/MBq to gallbladder and small intestine from the human data is very close to 0.17 cGy/MBq for the small intestine only based on rat biodistribution data. This comparison of human- and rat-derived dosimetry estimations demonstrate the utility of the rat as a human model at least for perfusion agents.

In Table 6, estimates of the absorbed radiation dose to humans from ^{99m}Tc-teboroxime are compared with those of another perfusion imaging agent ^{99m}Tc-hexamibi for which the data are available for both rest and stress studies in normal volunteers. Although the blood flow to the myocardium and the cardiac output and its distribution differ significantly between rest and stress, there appears to be no difference in the radiation dose estimates for ^{99m}Tc-hexamibi. Thus, we do not expect that the radiation doses from ^{99m}Tc-teboroxime will differ for rest and stress conditions, nor do we believe that there will be differences in dose estimations between the normal volunteers and patients in which the cardiac output might be significantly different. A large change in liver and gastrointestinal function, however, can lead to a major change in dose estimations.

The results show that the gallbladder and upper large intestine are the target organs and will receive respectively 26.5 and 33.2 μGy/MBq (98 and 123 mrad/mCi) ^{99m}Tc-teboroxime if the gallbladder empties every 6 hr. The dose to gallbladder decreases with shorter emptying intervals,

TABLE 6
Comparison of Absorbed Radiation Dose Estimates to Humans from ^{99m}Tc-Teboroxime and ^{99m}Tc-Hexamibi

Organ	Absorbed Dose in cGy/1110 MBq or rads/30 mCi Teboroxime (Cardiotec) Rest	Hexamibi (Cardiolite) Rest	Hexamibi (Cardiolite) Stress
Gallbladder wall	2.94	2.44	2.89
SI	2.38	2.89	2.78
ULI	4.35	4.77	4.66
LLI	3.09	3.33	3.22
Heart wall	1.32	0.53	0.57
Kidneys	0.66	2.01	1.67
Liver	1.90	0.59	0.43
Lungs	0.83	0.28	0.26
Spleen	0.49	0.60	0.48
Thyroid	0.34	0.63	0.81
Ovaries	1.25	1.33	1.22
Testes	0.34	0.31	0.29
Red marrow	0.55	0.77	0.72
Urinary bladder wall	0.90	1.89	1.55
Total body	0.54	0.49	0.46

however, the dose to upper large intestine remains almost constant and will be the limiting factor.

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