Radiation Dose from Radiopharmaceuticals Contaminated with Molybdenum-99

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Sixteen patients undergoing routine nuclear imaging procedures were injected with ^{99m}Tc-labeled radiopharmaceuticals containing ^{99}Mo which exceeded the recommended limit of 1 μCi of ^{99m}Mo per mCi of ^{99m}Tc. The kinetics of the resulting ^{99}Mo distribution in 14 of these patients were studied over a period of several weeks. The mean biologic half-life [$T_{1/2b}$] ranged from about 19.3 days to 11.2 days depending on the model used. Similarly, the mean radiation dose to the liver ranged from ~0.02 rad/μCi of ^{99}Mo to 0.05 rad/μCi of ^{99}Mo.

The range of values in the literature for biologic half-life and organ uptake leads to dose estimates for administered molybdenum-99 (^{99}Mo) which differ widely (*1–16*). There is also some disagreement as to the critical organs. The following paper presents clinical data on the kinetics and dosimetry of ^{99}Mo injected intravenously in association with technetium-99m (^{99m}Tc) as TcO$^-_4$ and in association with various radiopharmaceuticals used in clinical nuclear medicine procedures. This is compared with dosimetric information available in the literature.

METHOD

Sixteen patients were injected with ^{99m}Tc-labeled radiopharmaceuticals containing excessive quantities of ^{99}Mo because of a problem discovered after the injection. Fourteen of these patients were available for follow-up studies. Table 1 summarizes the patient data, the radiopharmaceuticals and the quantity of ^{99m}Tc administered. These patient doses were prepared from two separate elutions on consecutive days, of a generator consisting of fission product ^{99}Mo adsorbed on an alumina column. The occurrence of this problem highlights the need for careful checking of ^{99}Mo contamination from generators before administration of radiopharmaceuticals to patients.

The activity of ^{99}Mo administered to each patient was determined by two independent assays of the elution vials 7 to 11 days after the administration. These assays were carried out on a dose calibrator (Capintec CRC-17, Montvale, NJ), which had a ^{99}Mo calibration traceable to the National Bureau

of Standards. The two assays agreed with each other on the quantity of the ^{99}Mo administered to all patients to within 18% in the worst case and to within 10% in most cases.

The amount of ^{99}Mo delivered to the patients for each mCi of ^{99m}Tc administered was 170.4 ± 14.2 μCi/mCi for the first elution and 134.0 ± 12.5 μCi/mCi for the second elution, where the errors are the standard deviations of the results from the independent assays.

Calibration of Gamma Camera

Preliminary images established that the primary site of ^{99}Mo localization was the liver. Four liver phantoms were made up to accommodate the variability in patient size. The phantoms consisted of plastic jugs of 150, 510, 980, and 1,800 ml, respectively, which were filled with water containing a known amount of ^{99}Mo eluted from a generator column using a sodium hydroxide solution and then left for several days to reach equilibrium.

Several thicknesses of lucite (density = 1.05) simulated the attenuation of overlying tissue. A gamma camera fitted with a high sensitivity collimator and pulse height analyzer (PHA) set on a 20% window for the 140 keV emission from ^{99m}Tc was used to acquire the images. (It should be noted that with a collimated gamma camera there may be a problem in measuring the 140 keV gamma rays from ^{99m}Tc in the presence of high-energy ^{99}Mo gamma rays. If an auto-ranging multi-channel analyzer (MCA) is used to determine the location of the ^{99m}Tc peak, it may not be visible. This type of MCA scales its display to the largest signal in memory. High energy ^{99}Mo gamma rays are transmitted with little attenuation by the lead septa of the collimator, whereas the ^{99m}Tc gamma rays are greatly attenuated. Accordingly, with a collimator, the spectrum is dominated by the ^{99}Mo component and the ^{99m}Tc peak is suppressed. Without a collimator, the ^{99m}Tc peak is visible but not the ^{99}Mo peak, due, in part, to the greater interaction probability of the 140-keV gamma rays. The PHA window should therefore be adjusted with a pure

TABLE 1
Patient Data

Patient	Age	Dose Calibrator* Measurement of Tc-99m Activity Administered (mCi)	Estimated Mo-99 Activity Admin. (mCi)
Technetium-99m medronate-bone imaging			
A	41	20.0	3.52 ± 0.63
B	24	19.9	3.52 ± 0.63
C	68	19.0	2.22 ± 0.09
D	38	20.0	2.48 ± 0.10
E	46	19.9	2.63 ± 0.11
F	84	19.9	2.62 ± 0.11
G	68	19.8	2.74 ± 0.11
H	10	6.0	0.94 ± 0.06
Technetium-99m sulfur colloid-liver imaging			
I	75	4.0	0.47 ± 0.05
J	75	4.0	0.53 ± 0.04
K	75	4.0	0.59 ± 0.04
L	48	4.0	0.59 ± 0.04
Technetium-99m DTPA-kidney imaging			
M	1	3.0	0.40 ± 0.01
Technetium-99m MAA-lung imaging			
N	59	4.0	0.74 ± 0.09
Technetium-99m disofenin-gallbladder imaging			
O	38	5.0	0.74 ± 0.03
Technetium-99m-pertechnetate			
P	63	20.0	3.31 ± 0.21

*The dose calibrator was also responding to the ^{99}Mo component and thus would give an overestimate of the ^{99m}Tc actually administered.

^{99m}Tc source before the study to ensure that it is correctly centered).

All clinical measurements were performed using the 20% ^{99m}Tc peak to acquire acceptable images of kinetics data. This technique permitted the ^{99}Mo activity to be determined, as ^{99}Mo and ^{99m}Tc were in equilibrium at the time of measurement because the originally injected ^{99m}Tc had decayed leaving only the ^{99m}Tc produced by transmutation of the ^{99}Mo. The results in cps/μCi of ^{99}Mo for the four phantoms and the thicknesses of overlying material were used to translate the counting rate for each patient into μCi of ^{99}Mo localized in the liver with some correction for patient size and overlying tissue.

Standardization

In order to ensure that the data were being collected under the same conditions from day to day, an old ^{99}Mo generator core, giving approximately the same counting rate as the patients, was used as the standard. The time taken to collect 300,000 counts was noted using the same 20% ^{99m}Tc window as for the patient counts. Background was subtracted. As the study progressed, it became apparent that the core was not pure ^{99}Mo. The core decay data may be adequately described as the sum of two exponentials, one of which is assumed to be due to the decay of ^{99}Mo ($T_{1/2}$ = 2.75 days) and the other a

contaminant (or contaminants) with an apparent half-life of 10.2 ± 11.7 days. This contamination was not otherwise identified. The average difference between calculated and measured readings was ~1.8% with a maximum deviation of the measured from the theoretical data of 6.6%. Thus, counting errors due to instrument drift are assumed to be at most 7% and usually <2%.

Method of Determining Patient Activity

Data were acquired on 14 of the 16 patients with each patient providing between two and six measurements. These data, however, could not be acquired until 10–14 days after administration due to the delay in recognizing the nature of the problem and locating the patients for further testing. During this period, considerable redistribution of ^{99}Mo may have taken place as discussed below. Each patient was given a preliminary whole body survey to determine the localization of the ^{99}Mo. AP and PA images demonstrated that the liver was the only organ containing observable quantities of ^{99}Mo. Initially, the time taken to collect a 300,000 count image of the liver was noted. Later in the study, as the activity declined, the acquisition times became unacceptably long and 100,000- and 50,000- count images were collected. All data were corrected for background, and the net count-rate (counts/sec.) the determined. By use of the calibration data, this count rate was corrected to μCi of ^{99}Mo in the liver for each patient.

Methods of Data Analysis and Dose Estimation

The biologic data for each patient were initially fitted by a single exponential least squares fit which assumed that the ^{99}Mo was originally taken up and excreted by the liver.

For six of these patients (denoted by an asterisk in Table 2) the extrapolated activity at time of administration was determined to be greater than that assayed by factors which in general cannot be accounted for by experimental or calculational errors. Thus, the single exponential single compartment model is not appropriate.

A two-compartment model was derived in which the ^{99}Mo was assumed to be in two fractions, one of which was bound to the pharmaceutical and delivered to the radiopharmaceutical target organ [compartment A]; the remaining free ^{99}Mo being taken up directly by the liver [compartment B] (17). The experimental basis for the model is the finding that ^{99}Mo may tag directly to the radiopharmaceutical. (~70% for MDP and ~20% for sulfur colloid as determined by thin layer chromatography). A nonlinear least squares fit to the data for each patient was made using this model with the known administered dose and values for the free molybdenum fraction [f] 0.1, 0.2, 0.5, and 0.8. Dose estimates have been made for bone in the case of MDP, assuming that the radiopharmaceutical is equally distributed between cortical and trabecular bone (18). For sulfur colloid, it has been assumed that the radiopharmaceutical target organ is the liver since the radiopharmaceutical is released from the Kupffer cells only to be taken up by the polygonal cells. Thus, only liver dose is calculated for this agent.

Doses have been estimated using the MIRD tables (19) with ^{99}Mo S-factors which have been adjusted for pediatric cases (Cristy M., personal communication) where required. The dose from ^{99m}Tc in equilibrium with the ^{99}Mo (again using age adjusted S-factors) has been added to these dose estimates as it is not included in the published ^{99}Mo S-factors.

TABLE 2
Results Obtained from One and Two Compartment Models

Patient	Single exponential model			Two-compartment model											
				f = 0.8			f = 0.5						f = 0.1		
	Liver dose (rad)	Liver T_{eff} (hr)	Bone dose (rad)	Liver dose (rad)	Liver T_{eff} (hr)	Bone dose (rad)	Liver dose (rad)	Liver T_{eff} (hr)	Bone dose (rad)	Liver dose (rad)	Liver T_{eff} (hr)	Bone dose (rad)	Liver dose (rad)	Liver T_{eff} (hr)	Bone dose (rad)
B	78	46	0	—N/A—			68	36	17	43	35	36	36	34	31
C	57	52	0	—N/A—			50	45	12	32	43	18	27	42	20
D*	262	34	0	70	42	4	54	40	11	40	38	16	36	37	18
E	94	55	0	92	52	5	70	51	13	50	50	19	42	49	21
F*	125	45	0	81	46	5	60	44	13	42	42	13	37	41	25
G	81	61	0	—N/A—			72	55	15	50	53	15	42	53	25
H*	250	49	0	—See text—											
I	13	64	0	—N/A—			22	57	0	22	55	0	22	55	0
J*	75	42	0	23	55	0	25	56	0	24	49	0	25	52	0
L*	43	48	0	26	55	0	28	57	0	27	48	0	29	56	0
M*	387	41	0	85	56	0	58	59	0	32	57	0	25	54	0
O	14	55	0	23	46	0	17	44	0	12	42	0	10	41	0
P	79	62	0	—N/A—			—N/A—			—N/A—			—N/A—		

* The dose calibrator was also responding to the ^{99}Mo component and thus would give an overestimate of the ^{99m}Tc actually administered.

The dose from the original ^{99m}Tc administered in conjunction with the radiopharmaceutical has not been included.

RESULTS

The relationship of the data to the single and double exponential models is shown in Figure 1 for typical cases. The effect of applying a single exponential model to determine the initial activity results in an extrapolated activity at the time of administration which is anomalously greater than the total activity administered.

Table 2 summarizes the dosimetry results for the one- and two-compartment models. Both the single exponential and the double exponential model (with different assumed initial activities in the liver) give adequate fits to the data. This is true for all patients who were administered MDP with the exception of Patient H. In all cases, however, the single exponential fit gives a higher estimate of the administered dose than the double exponential model—particularly for patients D, F, and H.

Similar fits were obtained for the patients administered sulfur colloid. An example (Patient 1), is given in Figure 1B. For Patients J & L, however, the single exponential model severely overestimates the administered activity.
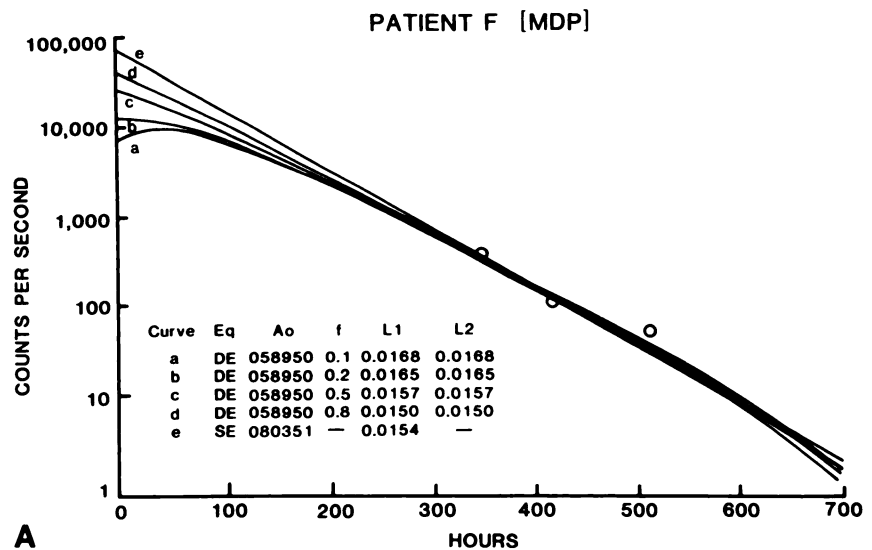
The results for the patients administered DTPA and DISIDA exhibit the same behavior, with the initial activity for Patient M being overestimated by a factor of ~5. The results for Patient P who was administered pertechnetate are shown in Figure 2 with a single exponential fit.
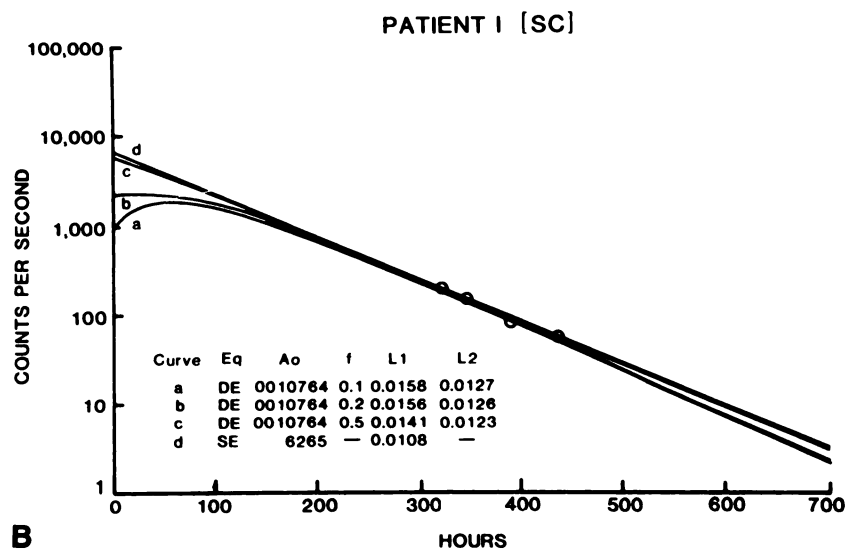
DISCUSSION

Sorenson (1-3) and Hennig (4) have examined the internal distribution of ^{99}Mo and agree that ~70–80% of the administered molybdenum is taken up by the liver. They are also in reasonable agreement with Rosoff and Spencer (5) concerning biologic retention giving biologic half-lives of the order of 10–40 days. An excellent review of human data is given by Cifka and Vesely (6).

In spite of this, reference publications (7–16) tabulate data which are in marked disagreement concerning the biological half-life, the target organ and the fraction of ^{99}Mo taken up in this organ.

The critical organs given in ICRP #2 (7) (kidney and GI tract) are the results of early studies (e.g., (20,21)) which were concerned with the effects of molybdenum in the diet of grazing animals. This information could also be applied to ingestion of radionuclides by workers. Thus, great attention was given to oral ingestion and absorption in the GI tract with the major route of excretion being through the kidneys. The Maximum Permissible Body Burden (MPBB) was derived on the basis that internal organs such as the liver, kidneys, etc. should not receive a dose rate in excess of 300 mrem/week as a result of this burden being *continuously* present in the whole body. Thus, the MPBB was critically dependent on the values which were assumed for the fraction absorbed from the GI tract, blood, etc. These values for man were in general not known and were therefore, inferred on the basis of work with animals. The MPBB can also be derived on the basis of the fraction of radionuclide present in the organ relative

PATIENT F [MDP]

Curve	Eq	Ao	f	L1	L2
a	DE	058950	0.1	0.0168	0.0168
b	DE	058950	0.2	0.0165	0.0165
c	DE	058950	0.5	0.0157	0.0157
d	DE	058950	0.8	0.0150	0.0150
e	SE	080351	—	0.0154	—

A

PATIENT I [SC]

Curve	Eq	Ao	f	L1	L2
a	DE	0010764	0.1	0.0158	0.0127
b	DE	0010764	0.2	0.0156	0.0126
c	DE	0010764	0.5	0.0141	0.0123
d	SE	6265	—	0.0108	—

B

FIGURE 1
Single exponential (SE) and double exponential (DE) least squares fits to the data obtained. The single exponential model gives a least squares fit to the initial activity A_0 and the effective decay constant $\lambda_{B_{eff}}$. The double exponential model gives least squares fit values to $\lambda_{A_{eff}}$ and $\lambda_{B_{eff}}$ using the known administered activity A_0 and assumed values of f, the fraction of contaminant taken up directly by organ B. $\lambda_{A_{eff}}$ and $\lambda_{B_{eff}}$ are the effective decay constants for compartments A and B. A: Patient F; B: Patient I.

to that in the total body. The values for the dose (rem/μCi) given for the ICRP#2 (7) data have been derived using a biologic half life of 45 days and recalculated for a single administration using a single compartment model with exponential elimination. From these data the dose to the liver (0.006 rem/μCi of administered ^{99}Mo) was calculated for the case of intravenous administration. The low value is due to the small fraction (0.1) of ^{99}Mo assumed to be absorbed from the blood.

The major discrepancy in biologic half-life can be ascribed to a typographical error by Kaul et al. (10) where the 20 day biologic half-life referenced from Sorenson (1–3) has been stated as 20 hr. This leads to an effective half-life of 15.4 hr giving a low estimate of liver dose (0.0089 rem/μCi) in NCRP 70 (6). The highest tabulated estimate of liver dose (0.05 rem/μCi) is given by ICRP 17 (9) because of the adoption of Sorenson's upper limit which assumes no biologic elimination at all. (It should be noted that the entry for ^{99}Mo in this reference under the heading of blood flow

in muscle, really refers to xenon-133. It also appears to be in error by a factor of 2.) The low estimate in ICRP #30 (14) is a result of the assumption that only 30% of the administered ^{99}Mo is taken up by the liver. The information in NCRP #65 (15) is taken directly from ICRP #2 (7) reworked to give a kidney dose of 0.012 rem/μCi. Cifka and Vesely (6) synthesized the relevant human data to derive a dose of 0.03 rem/μCi.

For the single exponential model, the present work has assumed that the biologic data gathered 10–14 days after administration reflects liver excretion. Thus, all patients have been included for this estimation of biologic and effective half-life (19.3 ± 7.4 and 2.1 ± 0.1 days, respectively). The estimate of liver dose (0.026 ± 0.003 rem/μCi) does not include the data from the six patients whose ^{99}Mo dose was clearly overestimated by this model. Similarly, only 11 patients have been included for the estimate of effective and biologic half-life using the two-compartment model (11.2 ± 2.0 and 2.2 ± 0.1 days, respectively). (One was excluded because
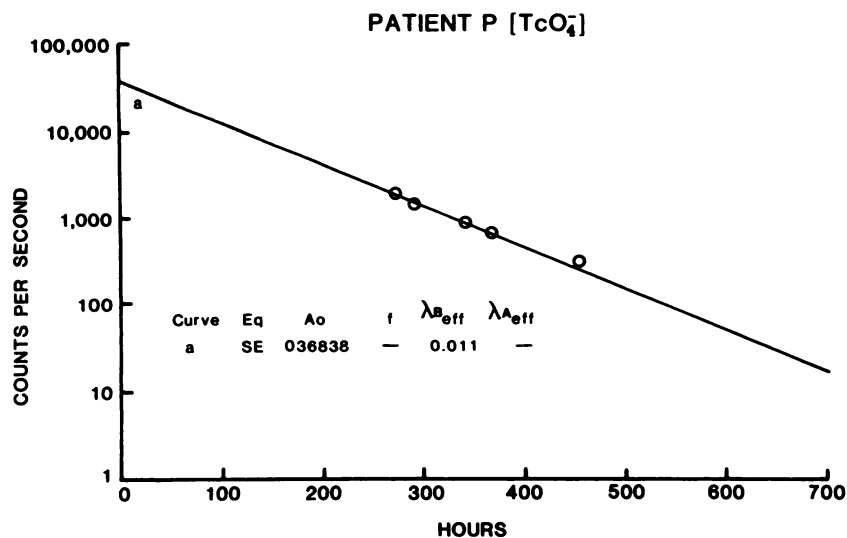
PATIENT P [TcO$_4^-$]

Curve	Eq	Ao	t	λ^B_{eff}	λ^A_{eff}
a	SE	036838	—	0.011	—

FIGURE 2
A single exponential (SE) least squares fit to the data obtained from patient P. The single exponential model gives a least squares fit to the initial activity A$_o$ and the effective decay constant $\lambda_{B_{eff}}$.

of a poor fit to the data; the other was administered TcO$^-_4$ and therefore the application of the two-compartment model is not immediately obvious). The dose in rem/μCi of ^{99}Mo administered has been derived for each group of patients. This dose was determined to be 0.024 ± 0.003 rem/μCi for all except the sulfur colloid patients, which have a relatively high estimate of 0.046 ± 0.003 as a result of the assumption that all the administered radionuclide was taken up directly by the liver.

Although the two compartmental model gives adequate fits for all but one case, (Patient H), it is unlikely that ^{99}Mo is excreted by the simple exponential mechanism described. It is more likely that there are several components to the release from both the radiopharmaceutical target organ and the liver. A simple model of this type (17) assumes a slow degradation of the radiopharmaceutical in the target organ after which free ^{99}Mo is cleared from the organ to be taken up by the liver, i.e., a slow component followed by a fast component. There is, however, little information in the literature on the long-term fate of bone-seeking agents or sulfur colloid as these agents have mostly been studied using ^{99m}Tc which decays too quickly for useful data to be obtained. Consequently, doses have not been calculated using this model.

Although not directly comparable with the data previously given in the literature, the results of this work point to the liver as the principal target organ for ^{99}Mo and provide dose estimates and biologic and effective half-lives in good agreement with other human data. The range of dose estimates available in the literature can also be understood.

The problem of dose estimation in the case of ^{99}Mo contamination of a radiopharmaceutical still requires a great deal of work. For example, the degree of ^{99}Mo tagging to clinically used ^{99m}Tc-labeled radiopharmaceuticals prepared as used clinically should be deter-

mined and the kinetics of well-defined ^{99}Mo-tagged radiopharmaceuticals should be studied in an animal model.

Clinically, in cases where molybdenum is inadvertently administered to patients in excess of allowable limits, not only should the amount of administered ^{99}Mo be determined, but the radiopharmaceutical should also be evaluated chromatographically to determine the fraction of bound ^{99}Mo. Biologic measurements should be initiated as soon as possible, preferably within 24 hr of administration to determine the way in which ^{99}Mo is taken up and excreted by the target organ and total body with both ^{99m}Tc and ^{99}Mo settings on the PHA. If this is not done the dose initially localized in the liver may be overestimated by using an extrapolated single exponential. Similarly, information taken at random from the literature may cause dose estimates to be considerably in error.

For prospective dose evaluation a value of 0.02–0.04 rem/μCi of administered ^{99}Mo (depending on the radiopharmaceutical involved), with a biologic half-life of 10–40 days, would seem appropriate. For accurate individual results, the procedures described above should be followed in order to take account of the considerable variations in biology and radiopharmaceutical tagging.

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