Radiation Doses from Technetium-99m DTPA Administered as an Aerosol

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A model is presented which enables radiation doses following the administration of technetium-99m diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA) aerosol to be calculated. The organ with potentially the highest radiation dose is shown to be the bladder wall. Radiation doses to the lungs, kidneys, and bladder wall and the effective whole-body dose are discussed in terms of the lung clearance rate of [^{99m}Tc]DTPA aerosol and the pattern of bladder voiding. The model indicated the influence of urine flow rate on bladder dose assuming a critical volume at which bladder voiding occurs. It is concluded that significant reductions in radiation doses may be achieved by encouraging patients or subjects undergoing investigations using [^{99m}Tc]DTPA aerosols to drink freely following the study.

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The use of technetium-99m diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA) inhaled as an aerosol of submicron sized particles has rapidly established itself in the measurement of pulmonary alveolar epithelial permeability (*1*), and for ventilation scintigraphy in the diagnosis of pulmonary embolism (*2*). Technetium-99m DTPA, when inhaled, crosses the alveolar membrane and is cleared by the kidneys in the same manner as an intravenously administered dose of the same compound. Data have been published recently (*3*) on the biological distribution and excretion of [^{99m}Tc]DTPA following i.v. administration. The clearance half-life of aerosolized [^{99m}Tc]DTPA in the lungs may vary considerably. In normal, nonsmokers it is ~60 min, but may be as short as 20 min in smokers, or in patients with lung disease (*4–6*).

A model is presented which enables radiation absorbed doses to be calculated, and indicates how they may be minimized.

METHODS

The model assumes that the aerosol in the lungs is uniformly distributed, and is exponentially eliminated. Thus,

$$L(t) = A_o \exp(-(\lambda_l + \lambda_p)t), \quad (1)$$

where L(t) is the activity remaining in the lungs at time t, A_o is the initial activity, λ_l is the biological rate constant and λ_p is the decay constant for ^{99m}Tc. Activity cleared from the lungs will accumulate in other parts of the body. Thomas et al. (*3*) assume that the activity in the remainder of the body (in this model, excluding kidneys, lungs, and bladder) is cleared in a bi-exponential manner, as is the activity in the kidneys. Thus,

$$R(t) = A_o \sum_{i=1}^{2} r_i \left(\frac{\lambda_l}{\lambda_{ri} - \lambda_l}\right) \times [\exp(-\lambda_l t) - \exp(-\lambda_{ri} t)]\exp(-\lambda_p t), \quad (2)$$

where R(t) is the activity in the remainder of the body at time t (excluding activity in the kidneys, lungs, and bladder), r_i (i = 1, 2) is the distribution coefficient of the ith component to the remainder of the body, and λ_{ri} (i = 1, 2) are the biological rate constants. Similarly,

$$K(t) = A_o \sum_{i=1}^{2} k_i \left(\frac{\lambda_l}{\lambda_{ki} - \lambda_l}\right) \times [\exp(-\lambda_l t) - \exp(-\lambda_{ki} t)]\exp(-\lambda_p t), \quad (3)$$

where K(t) is the activity in the kidneys at time t, k_i (i = 1, 2) is the coefficient of the ith component to the kidneys, and λ_{ki} (i = 1, 2) are the biological rate constants. The activity in the bladder at time t from, for

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example, the k_1 component is given by

$$B(t) = A_o k_1 \left[1 + \frac{\lambda_1 \exp(-\lambda_{k1} t) - \lambda_{k1} \exp(-\lambda_1 t)}{\lambda_{k1} - \lambda_1}\right] \times \exp(-\lambda_p t) \quad (4)$$

Similar expressions exist for the other components.

The cumulated activities in the lungs, $\tilde{L}$, remainder of the body, $\tilde{R}$, and kidneys, $\tilde{K}$, are obtained by integrating Eqs. (1), (2), and (3) with respect to time from t = 0 to infinity. Thus,

$$\tilde{L} = \frac{A_o}{\lambda_1 + \lambda_p} \quad (5)$$

$$\tilde{R} = A_o \sum_{i=1}^{2} r_i \frac{\lambda_1}{(\lambda_p + \lambda_{ri})(\lambda_1 + \lambda_p)} \quad (6)$$

$$\tilde{K} = A_o \sum_{i=1}^{2} k_i \frac{\lambda_1}{(\lambda_p + \lambda_{ki})(\lambda_1 + \lambda_p)}. \quad (7)$$

The activity in the bladder is assumed to accumulate over a period T, at which time the bladder is voided and re-fills. Integrating Eq. (4) from t = 0 to T gives B_1, the cumulated activity in the first cycle for component k_1

$$B_1 = A_o k_1 \left[\frac{1 - \exp(-\lambda_p T)}{\lambda_p} + \left(\frac{\lambda_1}{\lambda_{k1} - \lambda_1}\right) \times \left(\frac{1 - \exp(-(\lambda_{k1} + \lambda_p)T)}{\lambda_{k1} + \lambda_p}\right) - \left(\frac{\lambda_{k1}}{\lambda_{k1} - \lambda_1}\right)\left(\frac{1 - \exp(-(\lambda_1 + \lambda_p)T)}{\lambda_1 + \lambda_p}\right)\right]. \quad (8)$$

Similar expressions exist for the other components. Assuming the bladder is continuously re-filling and emptying over a constant voiding interval T, the cumulated activity in the bladder during the nth cycle is given by

$$B_n = \int_{(n-1)T}^{nT} B(t)dt - B((n-1)T) \int_0^T \exp(-\lambda_p t)dt. \quad (9)$$

Evaluating the expression gives

$$B_n = A_o k_1 \left[\exp(-(n-1)(\lambda_{k1} + \lambda_p)T)\left(\frac{\lambda_1}{\lambda_{k1} - \lambda_1}\right) \times \left(\frac{1 - \exp(-(\lambda_{k1} + \lambda_p)T)}{\lambda_{k1} + \lambda_p} - \frac{1 - \exp(-\lambda_p T)}{\lambda_p}\right) - \exp(-(n-1)(\lambda_1 + \lambda_p)T)\left(\frac{\lambda_{k1}}{\lambda_{k1} - \lambda_1}\right) \times \left(\frac{1 - \exp(-(\lambda_1 + \lambda_p)T)}{\lambda_1 + \lambda_p} - \frac{1 - \exp(-\lambda_p T)}{\lambda_p}\right)\right]. \quad (10)$$

The expression for B_n contains two parts, each the terms in a geometric progression. Summing the geometric progressions gives an expression for the total effective cumulated activity. Hence

$$\sum_{n=1}^{\infty} B_n = A_o k_1 \left[\frac{1}{1 - \exp(-(\lambda_{k1} + \lambda_p)T)}\left(\frac{\lambda_1}{\lambda_{k1} - \lambda_1}\right) \times \left(\frac{1 - \exp(-(\lambda_{k1} + \lambda_p)T)}{\lambda_{k1} + \lambda_p} - \frac{1 - \exp(-\lambda_p T)}{\lambda_p}\right) - \frac{1}{1 - \exp(-(\lambda_1 + \lambda_p)T)}\left(\frac{\lambda_{k1}}{\lambda_{k1} - \lambda_1}\right) \times \left(\frac{1 - \exp(-(\lambda_1 + \lambda_p)T)}{\lambda_1 + \lambda_p} - \frac{1 - \exp(-\lambda_p T)}{\lambda_p}\right)\right]. \quad (11)$$

Similar expressions exist for the other components.

Absorbed doses were calculated from this model using the "S" values (absorbed dose per unit cumulated activity) given in MIRD 11 (*7*). The source organs were assumed to be the lungs, kidneys, bladder contents, and the remainder of the body. The target organs considered were the lungs, kidneys, ovaries, testes, and the remainder of the body. The bladder wall doses were calculated separately. The S values for each target organ from remaining body activity were calculated by modifying the S values for the total body using the method of Roedler (*8*) and Cloutier (*9*).

$$S(\tau \leftarrow RB) = S(\tau \leftarrow TB)\frac{M_{TB}}{M_{RB}} - S(\tau \leftarrow L)\frac{M_L}{M_{RB}} - S(\tau \leftarrow K)\frac{M_K}{M_{RB}} - S(\tau \leftarrow BC)\frac{M_{BC}}{M_{RB}} \quad (12)$$

where τ is the target organ, RB is the remainder of the body, L is the lungs, K is the kidneys, BC is bladder contents, TB is total body, and M is mass. Thus,

$$M_{RB} = M_{TB} - M_L - M_K - M_{BC} \quad (13)$$

Absorbed doses for these target organs were calculated by multiplying the cumulated activities by the appropriate S values and summing for all source organs.

In calculating the dose to the bladder wall, the MIRD scheme assumes a constant bladder content of 200 ml. This is clearly unphysiological, and a model based on the more fundamental approach of Diffey and Hilson (*10*) was used. The method of Diffey and Hilson was modified in two ways. Firstly, to include a term in the equations describing the dose to the bladder to express the clearance of aerosol from the lungs, and secondly to adapt the presentation of the bladder dose data. Diffey and Hilson assume that the bladder is a sphere of radius r(t) and is filled by a constant urine flow rate F over a period T, at which time the bladder is

voided. They give curves of bladder doses for different flow rates plotted against voiding period. However, this can lose sight of unrealistically high bladder volumes implied when the flow rate is high and the voiding period is long. It was considered more physiological to assume that the urine flow rate and voiding period are related: that is, the bladder will be emptied when it has filled to some critical volume equal to FT. Thus, a low urine flow rate will lead to a longer voiding period and a high urine flow rate will lead to a short voiding period.

The absorbed dose from an initial activity of 1 mCi in the lungs, in the initial filling period, from component k_1 from photon irradiation is given by (*10*)

$$D_p = \frac{2\pi\Gamma f}{\mu F}\int_o^T B(t)\frac{1}{t}\left(1 - \frac{1-\exp(-2\mu r(t))}{2\mu r(t)}\right)dt, \quad (14)$$

where Γ is the exposure rate constant for ^{99m}Tc, μ is the energy absorption coefficient at 141 keV and f is the R to rad conversion coefficient for soft tissue. The radius of the bladder is given by

$$r(t) = \left(\frac{3Ft}{4\pi}\right)^{1/3} \quad (15)$$

The absorbed dose on the surface of the bladder from an initial activity of 1 mCi in the lungs, in the initial filling period, from component k_1, from conversion electrons and Auger electrons is given by (*10*)

$$D_e = \frac{1065.6\, n\bar{E}}{F}\int_o^T B(t)\frac{1}{t}dt, \quad (16)$$

In Eqs. (14)–(16) F is the urine flow rate in ml/hr, r is the radius of the bladder in cm, T is the bladder voiding period in hours.

The term $n\bar{E}$ represents the mean energy emitted per disintegration for electrons, and its value is given as 0.0173 MeV by MIRD 10 (*11*), 0.0156 MeV by NCRP 58 (*12*) and 0.0162 MeV by ICRP 38 (*13*). A value of 0.0162 MeV was taken. The integrations of Eqs. (14) and (16) were evaluated numerically using Simpson's rule. The total absorbed dose to the internal bladder wall is given by

$$D_T = \frac{\sum_{n=1}^{\infty} B_n}{B_1}(D_p + D_e). \quad (17)$$

Again, similar expressions exist for the other components which are summed. Table 1 summarizes all the data used in the appropriate units. With the units adopted, all doses are calculated in rad.

Absorbed doses were converted to dose equivalents by assuming a quality factor of 1. Values for the effective whole-body dose equivalent (the dose to the uniformly irradiated whole body which carries the same risk as the observed nonuniform dose) were calculated using the weighting factors quoted in ICRP 26 (*14*).

TABLE 1

Data from Thomas et al. (*3*), Diffey and Hilson (*10*), and ICRP 38 (*13*)

r_1	0.541	λ_{r1}	0.618 hr^{-1}
r_2	0.399	λ_{r2}	0.0746 hr^{-1}
k_1	0.0479	λ_{k1}	2.908 hr^{-1}
k_2	0.0122	λ_{k2}	0.0434 hr^{-1}
λ_p	0.1151 hr^{-1}		
Γ	0.72 R cm^2 hr^{-1} mCi^{-1}		
μ	0.027 cm^{-1}		
f	0.96		
$n\bar{E}$	0.0162 MeV		

RESULTS

The calculated doses, expressed as dose equivalent per unit activity, are given in Figs. 1–4, for different values of the lung clearance rate λ_l, and for different voiding periods. The main factors affecting bladder dose are the urine flow rate and the voiding period. Using the model adopted here, these are directly related in that an individual will empty the bladder when it has reached a critical volume, thus a low urine flow rate will also lead to a long voiding period. The results given in the figures assume that the bladder is initially empty, fills at a constant flow rate and is emptied once it has reached a volume of 500 ml (e.g., 200 ml/hr for 2.5 hr), and are calculated for a range of urine flow rates and consequent voiding intervals. For comparison the figures also give the calculated doses from i.v. administration using a similar model and similar data, but omitting the lung phase.

In Fig. 1 the dose to the lungs is seen to be independent of the bladder voiding period. Lung dose decreases as the lung clearance rate increases.

In Fig. 2 the dose to the kidneys is seen to be largely independent of the bladder voiding period. Kidney dose increases as the lung clearance rate increases.

The bladder dose is seen to increase significantly as the voiding period lengthens (Fig. 3). The faster the lung clearance rate, the more closely the bladder dose following aerosol administration approaches that following i.v. administration.

In Fig. 4 the effective whole-body dose is seen to increase as the bladder voiding period increases, since bladder doses dominate in the calculation. The effective whole-body dose from aerosol administration is very similar to that from i.v. administration: It varies very little as the lung clearance rate changes, except at very short bladder voiding periods.

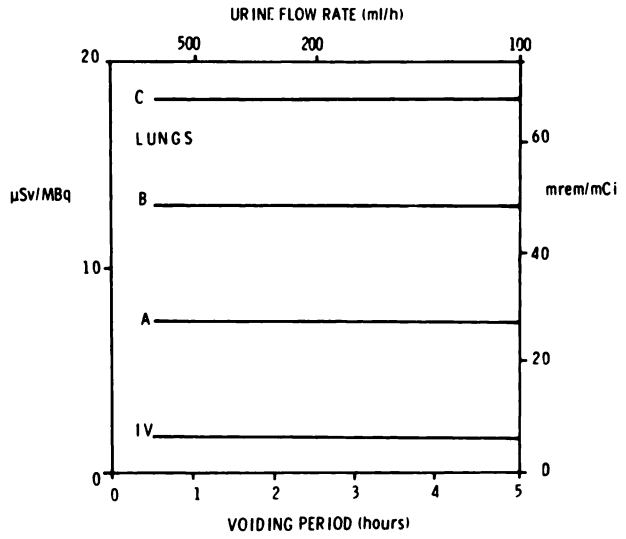

FIGURE 1
Dose-equivalent per unit activity from [^{99m}Tc]DTPA: Lungs. i.v.: Intravenous administration. A: Aerosol administration–lung clearance rate 2.079/hr ($T_{1/2}$ 20 min); B: Aerosol administration–lung clearance rate 1.040/hr ($T_{1/2}$ 40 min); C: Aerosol administration–lung clearance rate 0.693/hr ($T_{1/2}$ 60 min)

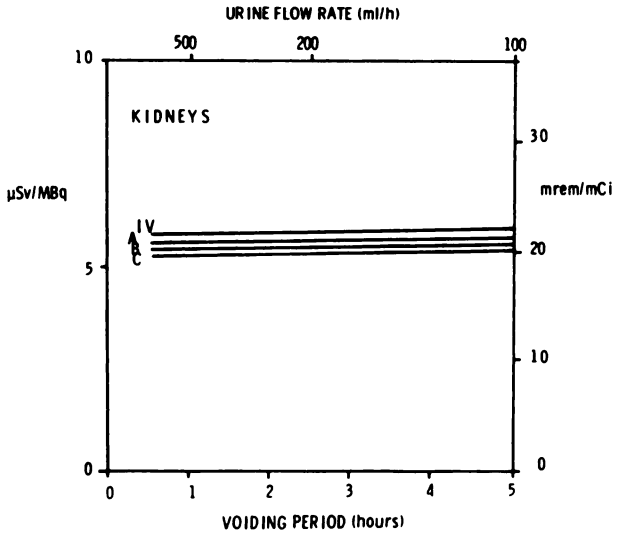

FIGURE 3
Dose-equivalent per unit activity from [^{99m}Tc]DTPA: Bladder wall. i.v.: Intravenous administration. A: Aerosol administration–lung clearance rate 2.079/hr ($T_{1/2}$ 20 min); B: Aerosol administration–lung clearance rate 1.040/hr ($T_{1/2}$ 40 min); C; Aerosol administration–lung clearance rate 0.693/hr ($T_{1/2}$ 60 min)

DISCUSSION

Plankey et al. (*15*) quote a lung dose following [^{99m}Tc]DTPA aerosol inhalation similar to that calculated by the model presented here, assuming a lung clearance half-time of 60 min (Fig. 1). However, they quote a bladder dose equivalent to 632 mrem/mCi (171 μSv/MBq), which is significantly larger than that presented here (Fig. 3), and would appear to ignore bladder voiding. The UK Administration of Radioactive Substances Advisory Committee (*16*) quotes a value of 28 mrem/mCi (7.5 μSv/MBq) for the effective whole-

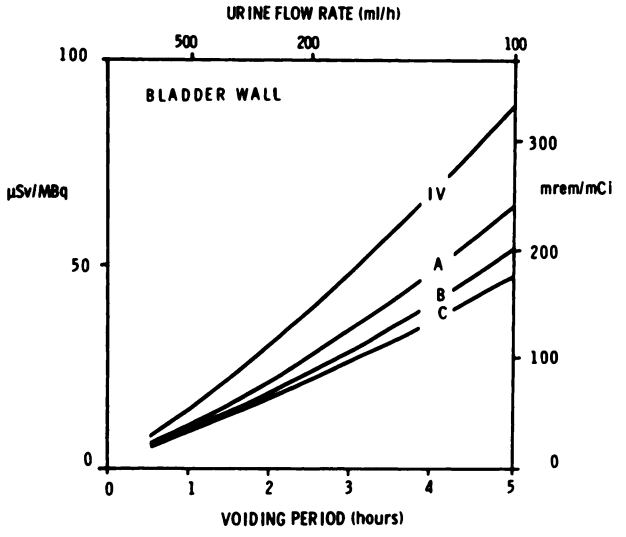

FIGURE 2
Dose-equivalent per unit activity from [^{99m}Tc]DTPA: Kidneys. i.v.: Intravenous administration. A: Aerosol administration–lung clearance rate 2.079/hr ($T_{1/2}$ 20 min); B: Aerosol administration–lung clearance rate 1.040/hr ($T_{1/2}$ 40 min); C: Aerosol administration–lung clearance rate 0.693/hr ($T_{1/2}$ 60 min)

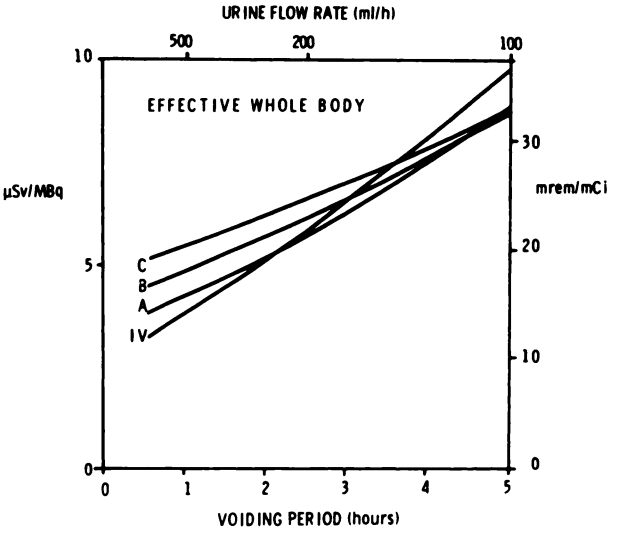

FIGURE 4
Dose-equivalent per unit activity from [^{99m}Tc]DTPA: Effective whole body. i.v.: Intravenous administration. A: Aerosol administration–lung clearance rate 2.079/hr ($T_{1/2}$ 20 min); B: Aerosol administration–lung clearance rate 1.040/hr ($T_{1/2}$ 40 min); C: Aerosol administration–lung clearance rate 0.693/hr ($T_{1/2}$ 60 min)

body dose equivalent, which is largely in agreement with the values calculated here (Fig. 4), but no details are given of how the figure was obtained.

Whole-body effective dose equivalents following administration of [^{99m}Tc]DTPA aerosols are seen to be remarkably similar for a wide range of lung clearance rates, and also very close to the values obtained following i.v. administration. The main contribution arises from the dose to the bladder wall. The general MIRD scheme assumes a constant bladder content of 200 ml: The model presented here allows calculations to be made for a changing bladder volume. Thus, account can be taken of different urine flow rates, different voiding periods, and different initial bladder volumes.

The model of Thomas et al. (*3*) for [^{99m}Tc]DTPA administered intravenously assumes that the remaining body activity and the kidneys act as parallel compartments clearing directly into the bladder. This is not strictly physiological as these compartments act in series. However, their figures are used here since they are the most recently published data and are presented as an official MIRD report. The organ with potentially the highest individual radiation dose is the bladder wall, and bladder doses will not be significantly in error by making this assumption.

The calculations for bladder dose are presented in a different way from Diffey and Hilson (*10*). The data here are expressed in terms of the concept of a critical volume at which bladder voiding occurs: Urine flow rate will determine the voiding period given this critical volume. Using this model, bladder doses are seen to be strongly dependent on urine flow rate since a low flow rate will lead to a high radioactive concentration in the bladder, and also lead to long voiding intervals. Thus, large reductions in radiation dose can be readily achieved by encouraging patients or subjects undergoing investigation using [^{99m}Tc]DTPA aerosols to drink freely following the study.

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