Radionuclide Kinetics in MIRD Dose Calculations

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A recent case report is reviewed and an alternative model for the radionuclide kinetics is presented; it estimates in an absorbed dose differing by a factor of two from the published calculation. Both models are consistent with observed data. Within a compartment model, one may choose to monitor a compartment of interest directly, or to monitor another compartment and (indirectly) solve for the activity in the compartment of interest. Advantages and disadvantages are reviewed.

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The MIRD publications (*1*) present methods for absorbed dose calculations from biologically distributed radionuclides. The method is continually being refined, and additional publications are periodically released by the MIRD committee to make the method more accurate and convenient. It remains, however, for the clinician or physicist to determine the distribution and kinetics of the radionuclide, factors that can have a substantial effect on the calculated absorbed dose. We wish to review a recently published case report, the cumulated activity calculated in that report, and an alternative cumulated activity based on the same data, but using a different model for the kinetics. The resulting absorbed dose differs by a factor of almost two depending on which model is assumed for the kinetics. We further use this case to illustrate advantages and disadvantages in the choice between direct monitoring of an organ, or inferring the activity in an organ from monitoring another compartment in the model.

Let us consider the patient data published by Nusynowitz et al. (*2*) for a case of medullary thyroid carcinoma with diffuse lung metastases. The patient had undergone total throidectomy followed by 5600 rads of external radiation to the neck and mediastinum. Approximately one year later a tracer dose of radioiodine showed no uptake in the neck or eyes, but both lungs concentrated radioiodine strongly. Further tests strongly suggested that the pulmonary lesions were metastatic medullary carcinoma of the thyroid. The patient was treated with a large dose of I-131 (321 mCi), following which there was temporary symptomatic improvement.

MODEL 1

The kinetics used in the original publication will be described first. The uptake of the tracer dose was diffuse throughout the lungs, and rather than any individual lesion, the lungs as a whole were chosen as the target organ for the MIRD dose calculation. Since there was no observed uptake in the neck, iodine concentration in the thyroid was considered negligible. In this case the radiation to the lungs came from two distributed sources: (a) the lungs themselves, and (b) the rest of the body. To perform the calculation, the clinician or physicist must determine the cumulated activities in these two sources. The uptake in the lungs was measured at 24 hr to be 12.6% without attenuation correction. When tissue attenuation was included, the uptake was estimated at 31.5%. After the therapeutic dose of iodine, the total urine output was collected daily. The radioactivity in the collected urine was measured to calculate the fraction of the administered dose of nuclide cleared per day. The total-body retention of nuclide was calculated as the administered dose minus the total amount cleared and is shown in Fig. 1. In order to calculate the cumulated activity in the lungs, it was assumed that the ratio of the amount of nuclide in the lungs to the amount of nuclide in the total body remained constant at 31.5% (the estimated 24-hr value from the tracer dose). Based on this assumption, the amount of nuclide in the lungs as a function of time is also shown in Fig. 1, both of whose curves show biological clearance only. The nuclide kinetics represented by these curves, when combined with physical decay were used in Ref. 2 to calculate the cumulated activity in the lungs and in the rest of the body. These cumulated activities were used by the MIRD method to calculate a dose to the lungs from the lungs of 3696 rads, and a dose to the lungs from the rest of the body of 179 rads. The total dose to the lungs from both sources was 3875 rads.

MODEL 2

An alternative model for the nuclide kinetics is represented by the compartment model shown in Fig. 2. This model includes a number of simplifying assumptions. Since there was no measured uptake in the neck, any iodine concentration in the thyroid is neglected and there is no thyroid compartment in the model. Compartment 1, which is labeled "nonlung", is principally blood. Other tissues that may take up iodine are neglected. Compartment 2 is the two lungs. The total-body iodine is the sum of the lung compartment and the nonlung compartment. Compartment 3 is the urine. We also assume that all the iodine is cleared through the

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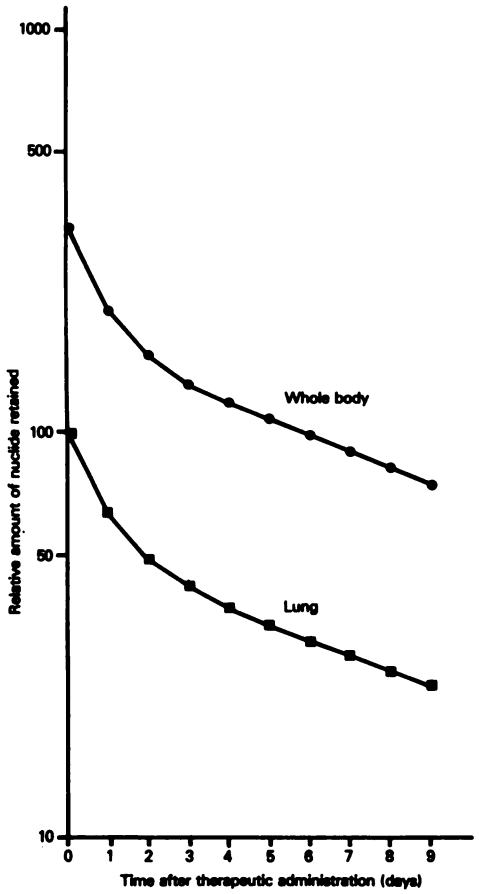

FIG. 1. Iodine kinetics based on Model 1. Physical decay has been corrected for, so that only biological elimination is shown in graphs. Squares represent pulmonary retention of nuclide; solid dots that in rest of body.

urine and we neglect any other pathways such as saliva, sweat, or stool. At time zero, the amount of nuclide in the lungs is zero, and the administered dose appears as a bolus in the nonlung compartment. Iodine is then picked up by and cleared from the lungs with rate constants k_{12} and k_{21}. The rate constant for clearance from the blood to the urine is k_{13}. The general method of compartment modeling has been discussed by a number of authors (*3–9*) and others. We apply the general solution to this simplified model.

If we let $q_b(t)$ be the amount of nuclide in the blood (nonlung), and $q_l(t)$ be the amount of nuclide in the lungs, then the differential equations describing this system are:

$$\frac{dq_b}{dt} = q_l k_{21} - q_b(k_{12} + k_{13}) \quad (1)$$

and

$$\frac{dq_l}{dt} = q_b k_{12} - q_l k_{21} \quad (2)$$

These two equations have the general solution:

$$q_b(t) = Ae^{-\alpha_1 t} + Be^{-\alpha_2 t} \quad (3)$$

and

$$q_l(t) = Ce^{-\alpha_1 t} De^{-\alpha_2 t} \quad (4)$$

where

$$\alpha_1 + \alpha_2 = k_{12} + k_{21} + k_{13} \quad (5)$$

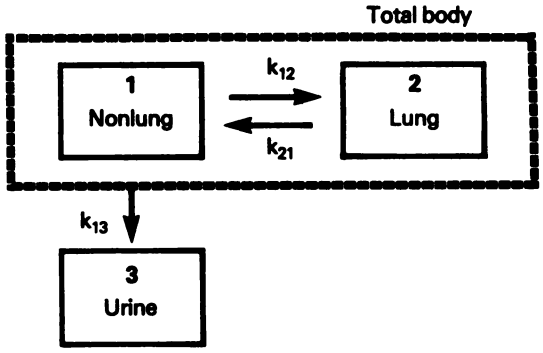

FIG. 2. Compartmental representation of Model 2.

and

$$\alpha_1\alpha_2 = k_{21}k_{13} \quad (6)$$

If we impose the initial conditions that at t = 0, there is no nuclide in the lungs and a bolus of nuclide, Q, appears in the blood, we have:

$$q_l(0) = 0 \quad (7)$$

and

$$q_b(0) = Q \quad (8)$$

Using these two conditions it can be shown that Eqs. (3) and (4) reduce to:

$$q_b(t) = Q\frac{(k_{12} + k_{13} - \alpha_2)e^{-\alpha_1 t} + (\alpha_1 - k_{12} - k_{13})e^{-\alpha_2 t}}{\alpha_1 - \alpha_2} \quad (9)$$

and

$$q_l(t) = Q\frac{k_{12}(-e^{-\alpha_1 t} + e^{-\alpha_2 t})}{\alpha_1 - \alpha_2}. \quad (10)$$

The total-body retention of nuclide at any time is given by the sum of the amount of nuclide in the nonlung compartment and the amount in the lung compartment

$$q_{tb}(t) = q_b(t) + q_l(t) \quad (11)$$
$$= Q\frac{(k_{13} - \alpha_2)e^{-\alpha_1 t} + (\alpha_1 - k_{13})e^{-\alpha_2 t}}{\alpha_1 - \alpha_2}$$

Equations (9) through (11) describe the kinetics of the administered dose of nuclide. If this is a radioactive nuclide, the activity as a function of time is described by equations similar to these, but the right side of each equation must be multiplied by $e^{-\alpha_3 t}$, where α_3 is the physical decay constant. If $q_l^*(t)$ represents activity in the lung compartment, then:

$$q_l^*(t) = e^{-\alpha_3 t}Q\frac{k_{12}(-e^{-\alpha_1 t} + e^{-\alpha_2 t})}{\alpha_1 - \alpha_2}, \quad (12)$$

and if $q_{tb^*}(t)$ represents activity in the total body, then:

$$q_{tb}^*(t) = e^{-\alpha_3 t}Q\frac{(k_{13} - \alpha_2)e^{-\alpha_1 t} + (\alpha_1 - k_{13})e^{-\alpha_2 t}}{\alpha_1 - \alpha_2}. \quad (13)$$

MIRD dose calculations require the cumulated activity in each compartment. The cumulated activity in the lung is given by the integral of Eq. (12):

$$\int_0^\infty q_l^*(t)dt = \frac{Qk_{12}}{(\alpha_3 + \alpha_1)(\alpha_3 + \alpha_2)}. \quad (14)$$

The cumulated activity in the total body is given by the integral of Eq. (13):

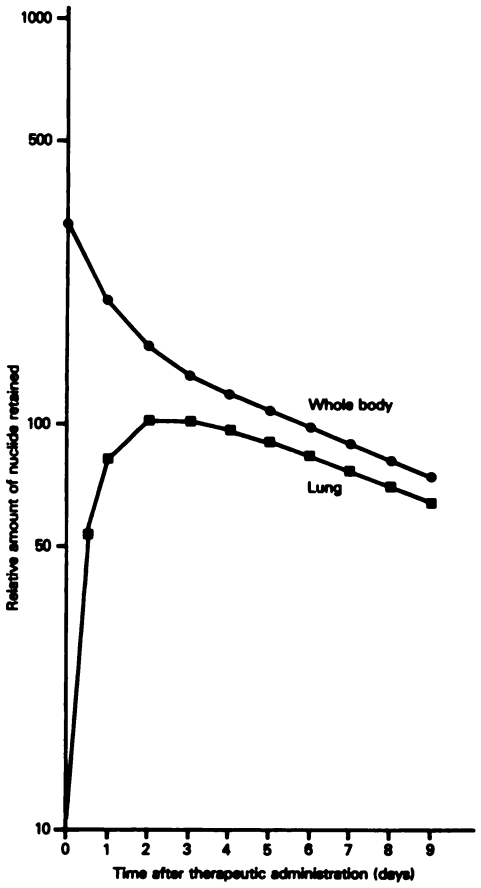

FIG. 3. Iodine kinetics based on Model 2. Physical decay has been corrected for only biological elimination is shown. Squares represent pulmonary retention; solid dots that in rest of body.

$$\int_0^\infty q_{tb}^*(t)dt = \frac{Q(\alpha_1 + \alpha_2 + \alpha_3 - k_{13})}{(\alpha_1 + \alpha_3)(\alpha_2 + \alpha_3)}. \qquad (15)$$

APPLICATION OF MODEL 2

Using Model 2, the uptake in the lungs can be calculated without ever monitoring the organ itself. Model 2, shown schematically in Fig. 2, has three unknowns: k_{12}, k_{21}, and k_{13}. From the measured total-body retention curve, three independent measurements can be extracted: the two exponential constants (α_1 and α_2), comprise two independent measurements, and the two intercepts comprise the third independent measurement. We note that the two intercepts provide only one independent measurement, not two, because they must add up to the administered dose. With three unknowns, and three independent measurements, in principle the system can be solved. The total-body curve is represented within Model 2 by Eq. (11). The exponential constants, α_1 and α_2, are read directly from the two components of the measured curve: $\alpha_1 = 1.10$/day, and $\alpha_2 = 0.087$/day. k_{13} can then be calculated from Eq. (11) using the intercepts: $k_{13} = 0.58$/day. One can generate k_{21} using Eq. (6), and k_{12} using Eq. (5): $k_{21} = 0.162$/day, and $k_{12} = 0.44$/day.

All the parameters in Model 2 are thus determined by the total-body retention curve. From these parameters a number of interesting results can easily be calculated. The fraction of the administered dose of nuclide in the lungs and in the whole body, as functions of time, are given by Eqs. (10) and (11), and are plotted in Fig. 3. The time of maximum activity in the lungs is found by setting the derivative of Eq. (12) to zero, which yields 1.9 days. The cumulated activity in the lungs is given by Eq. (14), which yields 690 mCi-days or 16 Ci-hr. The cumulated activity in the total body is given by Eq. (15), which yields 1080 mCi-days or 26 Ci-hr. The cumulated activity in the total body other than lung is the difference between these two: 10 Ci-hr. Using these cumulated activities in place of those derived from Model 1 yields a dose to the lungs of 7300 rads.

The fraction of the administered dose of nuclide in the lungs at 24 hr (from Eq. 10 and expressed as a percent) is 25%. This amount in the lungs is calculated solely from urine measurements after the therapy dose of radioactive iodine, and compares reasonably well with the direct measurement based on a tracer dose of radioactive iodine, which was reported as 31.5%

DISCUSSION

With an interest in calculating absorbed doses from internally distributed radionuclides, we have looked at published data for a single patient and two possible models for the radionuclide kinetics. We do not wish to argue that either model is correct, but rather to point out that large differences can result in the calculated absorbed dose (7300 rads compared to 3875 rads) depending on which model is used.

If the patient data can be represented by a compartment model, it may be possible to calculate the activity in an organ without direct monitoring of that organ. This was illustrated in Model 2, where only the urine activity measurements were used and the lung activity was calculated as a function of time. The limits of accuracy for direct monitoring, compared with the limits of accuracy for calculations based on other measurements within a compartment model, will depend on the particular case in question. For the patient data reviewed here, the uncertainty associated with direct monitoring may be significant. The uptake of a tracer dose at 24 hr was 12.6% before attenuation correction, and 31.5% after attenuation correction. It seems that such a large attenuation correction might introduce a significant uncertainty. The details of the attenuation correction were not presented. For the calculation based on only urine measurements within Model 2, if we assume an uncertainty of ±5% in each urine measurement, then standard propagation of error leads to an uncertainty of ±22% in the cumulated activity in the lungs. Again the size of this uncertainty will depend on the data observed for each particular case. If k_{12} is small relative to both k_{21} and k_{13}, then the value for k_{12} calculated from Eq. (5) will have a large relative uncertainty, and so will the value for the cumulated activity calculated from Eq. (14). If k_{12} is small, this leads to a small uptake in the lungs, and not surprisingly, in that case, it would be better to monitor the lungs themselves, rather than the urine. We see that considerations such as attenuation may introduce uncertainties in a direct measurement, while the actual rate constants observed in a particular case may lead to amplified uncertainties in calculations that do not involve direct measurements.

Finally, the kinetics of an organ system may not be the same in response to a therapy dose as in response to a tracer dose (*9*). Therefore it is an advantage to make pertinent measurements during the course of therapy, at which time direct monitoring of the organ might be difficult. Urine collection is possible during the course of therapy, but it is well known that a total urine collection is difficult. We suggest that daily blood samples are another indirect method that might be used during the course of therapy to generate a curve, which in this case could be corrected for physical decay and fitted to Eq. (9). The parameters determined by this fit could be used to calculate organ activities in a manner similar to what was done based on urine measurements above.

In summary, the choice of alternative models for radionuclide

kinetics can indicate large differences in the absorbed dose calculated—nearly a factor of two in the case reviewed here. Secondly, if the radionuclide kinetics can be represented by a simple compartment model, it may not be necessary to monitor directly the activity in a particular organ; instead, indirect measurements, such as on urinary output, may be sufficient to solve the equations. The uncertainties in an indirect method, such as with urine collections may be difficult to predict in advance, and one or two direct measurements of the lung, for example, would be valuable to verify that the model is reasonably accurate.

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