LETTERS TO THE EDITOR

Re: The Radiation Dosimetry of 2-[F-18]Fluoro-2-Deoxy-D-Glucose in Man

With the increasing variety of radiopharmaceuticals for human use and the attendant legislation controlling their application, studies designed to investigate their biokinetic behavior for purposes of radiation dosimetry are highly desirable, and publications such as that by Jones et al. (*1*) on the radiation dosimetry of ^{18}FDG are of unquestionable value. The radiation dose estimates in this paper, however, incorporate a fundamental error that often occurs in similar publications. The dose values presented for most of the listed organs have been overestimated in the sense that all, or part, of their cumulated activity has been accounted for twice. This error arises because the residual cumulated activity in the remainder of the body, after allowance for the sum of cumulated activities in named source organs ($\tilde{A}_{rem} = \tilde{A}_{TB} - \Sigma\tilde{A}_s$), has been used in conjunction with the S value for the total body ($S_{t\leftarrow TB}$) to calculate the effect of $\tilde{A}_{rem}$ on the dose to target organs, which have also been considered as source organs. However, it is implicit in that application of $S_{t\leftarrow TB}$ that the associated activity is uniformly distributed in the total body, including all source organs whose self-dose has been calculated independently. The dose to such a source organ will be overestimated by the self-dose that organ would receive from its relative proportion of $\tilde{A}_{rem}$ (i.e., $\tilde{A}_{rem}m_s/m_{TB}$). Thus in the reference paper, doses of the named organs have been overestimated by some 15–22 mrad/mCi, except those to the brain and heart, for which S values were calculated by the authors and which provide the clue to the error in question. In view of the uncertainty in the biokinetic data and the resultant assumptions inherent in the biokinetic model, these errors in dosimetry may prove relatively trivial in many circumstances. Nevertheless, the lack of complete biokinetic information should not lead to neglect of the basic physical principles of the current methods for accurate internal dosimetry.

The above error can be avoided by calculating an S value to be used with the accumulated activity in the remainder of the body ($\tilde{A}_{rem}$), given by:

$$S_{t\leftarrow rem} = \frac{m_{TB}S_{t\leftarrow TB} - \sum m_s S_{t\leftarrow s}}{m_{rem}},$$

and t and s represent target and source organs, and $m_{rem} = m_{TB} - \Sigma m_s$. This principle has been lucidly described by Cloutier et al. (*2*) and discussed at length by Roedler and Kaul (*3*).

In addition, the contribution to organ doses from bladder contents (Table 5, Ref. *1*) appears to have been estimated using a value of about 420 μCi-hr per mCi for $\tilde{A}_{BC}$, the cumulated activity in bladder contents, which is inconsistent with the mean value of about 200 μCi-hr per mCi observed in ten patients (Table 2, Ref. *1*). This discrepancy notwithstanding, the stated bladder contribution is ten times too high for the lungs and ten times too low for the ovaries.

An alternative approach would be to use the urinary excretion data to estimate average total-body retention. Thus the empirical formula:

$$R_{TB} = 0.7 + 0.075\,e^{-3.6t} + 0.225\,e^{-0.47t}, \quad (t \text{ in hr})$$

which is satisfactory for dosimetry purposes, leads to a urinary output curve and cumulated activity closely approximating the average data observed by the above authors (Fig. 1, Ref. *1*) if it is assumed that urine is the only significant excretory route for F-18 administered as ^{18}FDG. The advantage of this approach is that it not only permits an estimate of $\tilde{A}_{TB}$, and hence removes the guesswork from the estimate of $\tilde{A}_{rem}$, but also allows the use of analytical bladder models (*4*,*5*) that are convenient for estimating bladder-wall dose for any sequence of voiding periods. This approach confirms good linearity of $\tilde{A}_{BC}$ with duration of voiding period between 1 and 2 hr in the case in question, and hence of bladder-wall dose estimated using the MIRD bladder model based on fixed bladder contents of 200 ml. However, for shorter voiding periods it is reasonable to expect smaller urine volumes, and when urinary flow rate is taken into account—as in the bladder model proposed by Snyder and Ford (*6*)—it can be shown that reducing the voiding period to spare the dose to the bladder wall is not as effective as a direct linear relationship would suggest (*7*).

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Reply

Several points have been raised by T. Smith's letter concerning our work on the human radiation dosimetry of 2-[F-18]fluoro-2-deoxy-D-glucose (2FDG) in man (*1*). First, let us say that the concerns raised by T. Smith are welcome, and, we believe, are the

result of a thorough description of the methods used in estimating radiation dose that are presented in our paper. Much radiation dosimetry is presented in the literature and in product brochures as merely results with no statement of the assumptions and methods used, an unfortunate situation that can lead to misunderstandings and misinformation.

The first point raised is that the radiation dose is overestimated because S values from the total body to the target organ are used instead of S values from the remainder of the body to the target organ. It is correct that this leads to an overestimate in the radiation dose from the total body presented in our Table 5 (*1*). Table 1 compares the results of total dose to the target organ using the theoretically correct formulation and the estimate that we used in our paper, which ignores this overestimate. This table also shows the difference and the percent difference between these two values. The differences for all the organs including the bladder are between 9 and 20 mrads/mCi and result in an overestimation of between 10 and 26%, except for the bladder. The overestimate in radiation dose to the bladder is 20 mrads/mCi or 4.5%. These results were obtained using the computer program, CAMIRD III (*2*).

The bladder is the critical organ for this procedure, even if a shortened voiding schedule is used. Because radiation safety guidelines are dictated by the critical organ dose, the small reduction in dose obtained by using the theoretically correct method has no effect on the use of 2FDG. In addition, the larger error in the estimate of 440 mrads/mCi due to biological variability overshadows the 4.5% reduction in dose obtained using the theoretically correct formula. In point of fact, the decrease of 4.5% for the bladder dose is minimal compared to the differences between the normal human subjects and the uncertainties in the estimate of radiation dose (including the uncertainties in the Monte Carlo calculation of the S value). For the other organs, the estimate of radiation dose, being based on animal biodistribution data, is even more uncertain.

According to Roedler (*3*) the approximate and formally exact solutions approach each other as the relative cumulated concentration in the target compared with the total body increases, which is the case for the bladder compared with the other organs, and for photon energies above 100 keV, which is the case for F-18. For these reasons, we chose to overestimate the doses using the computationally simpler formula for our publication.

The second point raised by T. Smith was that the cumulated activity of 420 μCi-hr for the bladder contents was used to calculate the contribution of the bladder activity to the radiation dose for the other organs. This cumulated activity corresponds to the assumption that 16% of the injected dose is present in the bladder at injection time and that it disappears only by physical decay. This value is based upon dog biodistribution studies used to obtain approval for the human use of 2FDG and represents an intentional overestimate.

TABLE 1. COMPARISON OF RADIATION DOSES FROM 2FDG USING APPROXIMATE AND THEORETICALLY CORRECT FORMULA

Target organ	Approximate formula	Theoretically correct formula	Difference	Percent reduction
	mrad/mCi	mrad/mCi	mrad/mCi	(%)
Kidneys	85	71	14	16
Lungs	76	60	16	21
Liver	75	58	17	23
Spleen	160	144	16	10
Red marrow	51	42	9	18
Ovaries	70	56	20	26
Testes	68	54	14	21
Bladder	440	420	20	4.5

The errors in the lung and ovary dose due to bladder activity were traced to an error in S-value tabulation, and we apologize for this error. It is corrected in the table presented here and results in a change of total dose to the ovaries of from 53 to 70 mrads/mCi and in the lungs from 78 to 76 mrads/mCi.

We are pleased to have confirmation of the linear reduction in the dose for voiding periods between 1 and 2 hr, which T. Smith obtained. We would endorse an analysis, as he suggested in his last paragraph, that would take the varying bladder volume and activity into account in the calculation of radiation estimates. We do feel, however, that they would not result in any significant changes in the conclusions of our paper (*1*).

The items discussed here in no way change the qualitative conclusions of this study. We recommend, however, that the numerical results presented in this letter be used for dosimetry purposes. The dose estimate to the bladder of 420 mrads/mCi, for a 2-hr void, defines this organ as the critical organ. This dose estimate is based upon human retention data and avoids the assumptions inherent in using animal biodistribution data.

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Unmasking of Asymmetrical Renal Perfusion After Exercise in Unilateral Renovascular Hypertension

Radionuclide renography is an important noninvasive method for the evaluation of possible unilateral renovascular hypertension, but the false-negative rate for this investigation has variously been reported as 10–27% (*1*,*2*). In the course of investigating a patient with significant left renal-artery stenosis, the renogram was found to be normal at rest, but evidence of unilateral renal ischemia was seen when the procedure was repeated immediately after exercise, suggesting that this physiological stimulus may increase the sensitivity of radiorenography in detecting significant unilateral renal ischemia.

CASE REPORT

A 37-yr-old woman was first noted to be hypertensive in the middle trimester of her fifth pregnancy. She had no past history