Background Equivalent Radiation Time (BERT)

TO THE EDITOR: I applaud Dr. Cameron's new radiation unit, the BERT, or "background equivalent radiation time" (*1*). I would like to propose a companion unit, "environmental radiation normally incurred equivalent," or the ERNIE. With these two units, understanding radiation doses will surely become child's play.

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The Volume of Distribution of MAG_3

TO THE EDITOR: In a recent article in the *Journal*, Bubeck et al. (*1*) reported a distribution volume for MAG_3 of 7.05 liters and a protein binding in plasma of 90%. These values, however, seem incompatible with each other. Thus, for an extracellular fluid (ECF) volume of 14 liters per 1.73 m^2 (*2–5*), of which 3 liters is plasma, then, with 90% protein binding, the effective distribution volume would be 2.7 liters for the protein-bound agent (i.e., 90% of 3 liters) plus 1.4 liters for free agent (i.e., 10% of 14 liters), giving a total of 4.1 liters. Based on their data for plasma-protein binding of ortho-iodo-hippurate (OIH) (70%), corresponding values for OIH would be 2.1 and 4.2 liters, a total of 6.3 liters. In general, if we call the protein bound fraction x, then the effective volume of distribution of tracer in liters would be $3x + 14(1-x)$. So, for a distribution volume of 7.05 liters (MAG_3), this would indicate a protein binding of 63%, and for a distribution volume of 10.9 liters (OIH), a protein binding of 28%. From our own multiple blood sample data in 20 children with MAG_3 clearances ranging between 132 and 337 ml/min per 1.73 m^2, we obtained a MAG_3 distribution volume of 6.4 liters per 1.73 m^2, broadly similar to the values reported in adults and indicative of MAG_3 protein binding in plasma of 69%.

The first and likeliest explanation that comes to mind for this apparent discrepancy between MAG_3 distribution volume and protein binding is that protein binding in vitro overestimates protein binding in vivo. In a recent editorial, Jeghers et al. emphasize the hazards of extrapolating in vitro protein-binding data to the in vivo situation (*6*). Second, there may be bi-directional transport of MAG_3 into intracellular compartments, most likely red blood cells or liver. However, red cell binding is only 5% (*1*). The liver kinetics are less certain, although MAG_3 is an organic anion and may therefore undergo some bi-directional hepatic transport. Alternatively, ^{99m}Tc-labeled species may be exported from the liver. Third, it must be recalled that the ECF volume is a functional rather than anatomical volume and varies according to the tracer used to measure it, generally showing an inverse correlation with the molecular weight of the tracer. The ECF volume of 14 liters used here is based on ^{51}Cr-EDTA (380 Daltons) and ^{99m}Tc-DTPA (492 Daltons), which give larger ECF volumes than inulin (5000 Daltons) (*3,7*) but smaller ones compared with ^{77}Br (*8–10*). Technetium-99m-MAG_3 has a molecular weight of 376 Daltons, almost identical to ^{51}Cr-EDTA, while OIH has one of 310 Daltons. So, it would be difficult to sustain a larger volume of distribution for MAG_3 on the basis of molecular size.

One of the difficulties encountered in the MAG_3 literature is that authors do not always make clear their method of calculating volume of distribution. Different methods may explain the wide variation in reported values, from 4 liters (*11*) through about 7 liters (*1,12*) to 16 liters (*13*). The values quoted by Bubeck et al. (*1*) are based on Sapirstein's equation (*14*) and ours on Ladegaard-Pedersen's equation (*7*). These equations, which give identical values (Method A), both assume that the permeability coefficient of the tracer is the same in both directions across the endothelium. Another method available to calculate distribution volume (Method B) is to divide the clearance by the rate constant (α_2) of the second exponential,

$$V = \frac{\text{clearance}}{\alpha_2}. \qquad \text{Eq. 1}$$

This assumes that the concentration of tracer becomes uniform throughout the distribution volume, and, in particular, that it becomes equal in plasma and extravascular ECF. This approach overestimates distribution volume because, at equilibrium (i.e., when rate constants of tracer disappearance from plasma and extravascular ECF become identical), the extravascular tracer concentration is higher than the plasma concentration. Based on our MAG_3 data in children, this overestimation, compared with Method A, amounted to 44% (± s.d. 11). In the absence of renal function, the concentration in plasma and extravascular ECF would be expected to become equal and so, as would be anticipated, this overestimation correlated significantly with MAG_3 clearance.

An additional method occasionally described (Method C) gives an even greater overestimation of distribution volume. With this method, the injected dose is divided by the zero time intercept (B) of the second exponential. By ignoring the first exponential, it essentially assumes instantaneous mixing of tracer throughout its distribution volume.

Thus

$$V = \frac{\text{dose}}{B}. \qquad \text{Eq. 2}$$

By ignoring the first exponential, clearance becomes approximated to

$$\text{"clearance"} = \frac{\text{dose}.\ \alpha_2}{B}. \qquad \text{Eq. 3}$$

Therefore, substituting for dose,

$$V = \frac{\text{"clearance."}\ B}{B.\alpha_2} \qquad \text{Eq. 4}$$

$$= \frac{\text{"clearance"}}{\alpha_2}. \qquad \text{Eq. 5}$$

As can be seen by comparing Equations 1 and 5, Method C consequently overestimates Method B by an amount identical to the overestimation of clearance introduced by ignoring the first exponential. From our data, Method C overestimated Method B by 128% (±35), i.e., gave a distribution volume more than twice the "true" value (based on Method A). Again, the overestimation correlated with the clearance.

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REPLY: This statement is based on a fundamental misunderstanding: Peters and colleagues relate the plasma-protein binding of ^{99m}Tc-MAG_3 (reported by us to amount to 90%) to the total plasma volume of ~3 liters (i.e., 2.7 liters), whereas the term "plasma-protein binding" actually indicates the percentage of a substance in the plasma (=100%) bound to plasma proteins. Since 1 liter of plasma contains about 70 g of protein, this means that 90% of ^{99m}Tc-MAG_3 is bound to 210 g of protein and the remaining 10% are distributed "freely" in the plasma water. All data referring to the protein binding in plasma (*1–4*) are related exclusively to the intravascular space and estimations of the relative concentration of this substance in the remaining extracellular fluid can only be made if the measurement was performed under steady-state conditions, which was not the case.

The objection that the value we found was too high due to the fact that it was determined in vitro and thus could be overestimated according to the results of Jeghers et al. (*5*) does not apply. From an objective point of view, that publication (*5*) has been quoted incorrectly. Jeghers et al. have rightly drawn attention to the problem of precipitation reactions as well as to the protein fractions used in vitro, both of which can lead to incorrect results. In the same paper, however, Jeghers et al. demonstrated that there is a very good correlation of ultrafiltration measurements (three working groups, two methods, 85%–91%), a technique accepted by renal physiologists for many years (*6*). Moreover, we used patients' plasma for our measurements so that we had the complete range of proteins in the plasma and thus virtually performed in vivo investigations. The differences in pressure (≤5 bar) during the measurement procedure, as compared to the in vivo situation, have no effect on the degree of protein binding in plasma, since neither a covalent, nor an ionic, nor a Van-der-Waals interaction can be drastically influenced by physical factors of this type. However, it is definitely not possible to calculate the plasma-protein binding of an agent on the basis of the theoretical volume of distribution as Peters et al. have done.

In our study (*1*) although there may exist more realistic models (e.g., *7*), we applied the two-compartment model according to Sapirstein (*8*) to compare our results with regard to clearances, distribution volumes, and biologic half-lives to the results obtained by other authors (*2–4*). Our intention was not the calculation of "real" volumes of distribution, considering that this term has a different definition in each model and is, for instance, also used to describe the reciprocal value of a specific plasma concentration (*9*). What they have in common is that they are theoretical volumes of distribution that cannot be attributed to a true anatomic space, which is also stated by Sapirstein et al. (*8*). As found by Taylor et al. (*2*), we also were able to show (*1*) that according to the two-compartment model the biologic half-lives of orthoiodohippuric acid (OIH) and ^{99m}Tc-MAG_3 are identical in the respective compartments and that the volume of distribution of OIH is higher than that of ^{99m}Tc-MAG_3 by a factor of about 1.5 (on the basis of simultaneous plasma measurements). This results in a lower clearance of ^{99m}Tc-MAG_3 by the same factor as compared to OIH. We succeeded in confirming this theoretical assumption by simultaneous steady-state clearance measurements (*1*). The absolute values for the distribution volumes and for the clearances determined according to the model by Sapirstein do not, however, have to be identical for the different working groups, since they depend, among other factors, on the period of time during which blood sampling was performed.

In our opinion, it is not possible to calculate a "true" volume of distribution, especially during slope; these values mainly serve as a means to compare different substances and to compare relative results obtained with those of other authors using the same model.

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