

## 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.

## REFERENCE

1. Newsline (News Briefs). *J Nucl Med* 1991;32:26N-28N.

Paul S. Sirota

The Allentown Hospital/Lehigh Valley Hospital Center  
Allentown, Pennsylvania

## The Volume of Distribution of MAG<sub>3</sub>

TO THE EDITOR: In a recent article in the *Journal*, Bubeck et al. (1) reported a distribution volume for MAG<sub>3</sub> 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<sup>2</sup> (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<sub>3</sub>), 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<sub>3</sub> clearances ranging between 132 and 337 ml/min per 1.73 m<sup>2</sup>, we obtained a MAG<sub>3</sub> distribution volume of 6.4 liters per 1.73 m<sup>2</sup>, broadly similar to the values reported in adults and indicative of MAG<sub>3</sub> protein binding in plasma of 69%.

The first and likeliest explanation that comes to mind for this apparent discrepancy between MAG<sub>3</sub> 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<sub>3</sub> 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<sub>3</sub> is an organic anion and may therefore undergo some bi-directional hepatic transport. Alternatively, <sup>99m</sup>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 <sup>51</sup>Cr-EDTA (380 Daltons) and <sup>99m</sup>Tc-DTPA (492 Daltons), which give larger ECF volumes than inulin (5000 Daltons) (3,7) but smaller ones compared with <sup>77</sup>Br (8-10). Technetium-99m-MAG<sub>3</sub> has a mo-

lecular weight of 376 Daltons, almost identical to <sup>51</sup>Cr-EDTA, while OIH has one of 310 Daltons. So, it would be difficult to sustain a larger volume of distribution for MAG<sub>3</sub> on the basis of molecular size.

One of the difficulties encountered in the MAG<sub>3</sub> 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 ( $\alpha_2$ ) of the second exponential,

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

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<sub>3</sub> data in children, this overestimation, compared with Method A, amounted to 44% ( $\pm$  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<sub>3</sub> 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

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

By ignoring the first exponential, clearance becomes approximated to

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

Therefore, substituting for dose,

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

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

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% ( $\pm$ 35), i.e., gave a distribution volume more than twice the "true" value (based on Method A). Again, the overestimation correlated with the clearance.