Thiopental Anesthesia in the Elderly

Appropriate drug therapy of elderly patients is a matter of growing concern, and there is ample documentation that the frequency of adverse drug reactions increases in elderly patients. The difficulties inherent in caring for the elderly are compounded by the fact that most scientific studies of drug kinetics and response are conducted in the young, whereas therapy of older patients is often based on clinical impressions and anecdotal data. One clinical impression about anesthetic management of older patients is that the elderly are more sensitive to thiopental. In this issue, Homer and Stanski report a systematic investigation of the physiologic basis of this clinical impression.

The belief that elderly patients are more sensitive to thiopental is supported by the observation that the thiopental dose needed for induction of anesthesia decreases with age. Homer and Stanski correctly point out that this increased sensitivity could be due either to altered thiopental pharmacokinetics in elderly patients or to an age-related change in the pharmacodynamic relationship between biophase thiopental concentrations and response. The general clinical impression is that the aged brain is pharmacodynamically more sensitive to sedative, hypnotic, and anesthetic drugs. Homer and Stanski have evaluated this in a mathematically rigorous fashion that exemplifies recent advances in the application of kinetic methods to the analysis of drug effects. They have chosen the electroencephalographic measurement of leading spectral edge as an objectively quantifiable index of anesthetic drug effect. A separate "effect compartment" was used to correlate the onset and offset of changes in spectral edge with the increase and decrease in thiopental serum levels. This effect compartment can be thought of as the kinetically defined biophase of thiopental's central nervous system actions. A general concentration-response equation was used to relate these biophase concentrations to the observed changes in spectral edge and to calculate values for a parameter (IC$_{50}$) that represents the biophase thiopental concentration required to produce one-half of maximal electroencephalographic slowing. By demonstrating that the IC$_{50}$ is not affected by age, Homer and Stanski have provided impressive evidence that the aging brain is not unusually sensitive to the electroencephalographic slowing effects and, presumably, the anesthetic effects of thiopental. It is rarely possible to attach a physiologic significance to IC$_{50}$ measurements of this type. However, in a recent study of the antifibrinolytic effects of epsilon-aminocaproic acid (EACA), the soundness of this approach was supported by the fact that the estimate of $63 \pm 19.7$ mg/ml ($\pm$ SD) for the IC$_{50}$ agreed with the value of 0.55 nM or 72 mg/ml reported for the dissociation constant of the EACA-plasminogen complex.

Finding no apparent pharmacodynamic basis for the increased sensitivity of older patients to thiopental, Homer and Stanski have advanced a pharmacokinetic explanation for the phenomenon. They have used a three-compartment system to analyze thiopental disposition kinetics and report that the volume of the central compartment is reduced in the elderly. Since the central compartment constitutes the space in which an intravenous injection of thiopental is initially distributed, it can be thought of as serving the important function of buffering the intensity of central nervous system and cardiovascular responses during anesthetic induction with this agent. An age-related reduction in the volume of this compartment could thus be responsible for exaggerated initial central nervous system depression or hypotension in the elderly.

The anatomic basis for this pharmacokinetic observation requires further investigation. We have used a similar three-compartment system to model the distribution kinetics of urea, inulin, and several relatively polar drugs and have found that the volume of the central compartment is similar to expected values for intravascular space. The incorporation of inulin as a tracer in some of these studies yielded results suggesting that transcapillary exchange between the intravascular and interstitial fluid spaces is kinetically heterogeneous, accounting for the need for two separate peripheral compartments. It is possible that slow transcapillary exchange of polar compounds occurs through the interendothelial cell junctions of skeletal muscle and other continuous capillaries and that rapid transcapillary exchange occurs through the fenestrae of capillaries in the splanchnic bed. Alternatively, body tissues may contain both fast and slow equilibrating interstitial fluid components.

In applying this approach to an analysis of pentobarbital kinetics in dogs, we found that a three-compartmental system was also required to model the distribution...
kinetics of this barbiturate. However, the volume of the central compartment clearly exceeded that expected if the initial distribution of pentobarbital were confined to the intravascular space. Homer and Stanski reach a similar conclusion about the significance of the thiopental central compartment volume that they measured in young adults. They propose that, with aging, vessel-rich tissues included in this central compartment appear to “move” to more slowly equilibrating peripheral compartments. In this regard, an attractive hypothesis is that the volume of the central compartment shrinks progressively with aging until it approximates that expected for intravascular space.

Unfortunately, this hypothesis cannot be validated from the available data. Even when correction is made for the thiopental blood to plasma partition ratio of 0.88 reported by Jung and colleagues, some of the estimates of central compartment volume that Homer and Stanski report in elderly patients are less than expected values for intravascular space. In part, this may reflect the experimental approach used to measure central compartment volume. Early blood samples in these studies were obtained from an arterial site that was between the site of intravenous injection and peripheral capillary beds. This may have reduced thiopental mixing in sampled blood to the extent that estimates of central compartment volume were considerably less than intravascular space. The pertinence of these considerations is supported by recent demonstrations of the importance of injection and sampling site selection in the design of tracer studies. Homer and Stanski’s pharmacokinetic results also must be evaluated in the light of a previous report by Christensen and colleagues, who found that the volume of the central compartment of thiopental distribution remains unchanged in the elderly but that there is a reduction in the rate of thiopental distribution from this compartment to the fast equilibrating peripheral compartment. Reconciliation of these results awaits further study and elucidation of the anatomic and physiologic basis of age-related changes in thiopental distribution. However, both groups of investigators are correct in attempting to explain the increased sensitivity of elderly patients to thiopental anesthesia on the basis of changes in the initial distribution kinetics of this drug, rather than alterations in total distribution volume and elimination clearance. This approach is consistent with the generally accepted concept, first advanced by Brodie in 1952, that the brevity of anesthesia following intravenous injection of thiopental primarily reflects rapid redistribution of this drug, rather than its rate of metabolism and elimination.

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References