Title: THIOPENTAL KINETICS AND AGE: A REASSESSMENT

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Introduction. Several investigators have attempted to determine the basis of the increased reactivity of the elderly to thiopental. No age-related changes in pharmacodynamics have been found.[1,2] Rather, the increased reactivity of the elderly to thiopental has been attributed to age-related pharmacokinetic changes.[1,2] The purpose of the present study was to attempt to verify either the hypothesis that thiopental is transferred more slowly from the central to the fast compartment in the elderly[1] or the hypothesis that the central volume of thiopental is smaller in the elderly.[2] Either pharmacokinetic change with age would explain the increased central nervous system and cardiovascular sensitivity of older patients to standard doses of thiopental.

Methods. Twenty-one ASA Physical Status I or II males participated in this study after giving institutionally approved written informed consent. Seven patients were in each of the following age ranges: 20 to 45, 46 to 65, and 66 to 80 years. All underwent peripheral, nonvascular operative procedures while in the supine position. Most patients were premedicated with a narcotic alone or in combination with an antisialagogue. A radial artery was cannulated in all patients for blood sampling during the early phases of drug distribution while later samples were obtained from a catheter placed in a proximal arm vein (cephalic). A standard dose of thiopental, 3 mg/kg IV, was used; to ensure anesthetic induction with this dose of thiopental, preinduction IV sedation was titrated with either fentanyl (50-250 ug) or sufentanil (5-50 ug). The anesthetic was maintained with enflurane in N_2O/O_2 (F_IO_2 = 0.5); tracheal intubation was facilitated with IV vecuronium. The average duration of anesthesia was 3.4 ± 1.7 hours. The present pharmacokinetic models are based on blood samples obtained at 1, 2, 3, 5, 10, 15, 20, 30, 45, 60, 90, and 120 minutes after the start of thiopental administration, hourly thereafter to 10 hours, and at 12 hours. Plasma thiopental concentrations were measured using a high performance liquid chromatographic (HPLC) technique designed to minimize thiopental breakdown[3]; all samples were extracted in duplicate on the day of collection and analyzed within 36 hours. The disposition of thiopental was described with a three compartment open mammillary system using the CONSAM digital computer program.[4] The sum of the intercompartmental clearances (ΣCl_I) was calculated as a potentially useful index of interindividual variation in drug distribution.[5] Correlations between age and the kinetic variables were subsequently sought using standard techniques. The criterion for rejection of the null hypothesis was $P < 0.05$.

Results. The pharmacokinetic variables describing the disposition of thiopental in the present study are summarized in Tables 1 and 2. There was no relationship between age and any of these variables except Cl_F and ΣCl_I[5], of which Cl_F is a major part. These relationships are described by the following equations: $Cl_F = -0.038\ Age + 5.313$ ($r = -0.480$, $P < 0.05$) and $\Sigma Cl_I = -0.034\ Age + 5.635$ ($r = -0.434$, $P < 0.05$).

Table 1: Volumes of distribution of thiopental (L) x̄(S.D.)

V_C	V_F	V_S	Vd_{SS}
5.1	25	101	131
(4.7)	(10)	(42)	(44)

Table 2: Clearances of thiopental (L/min) x̄(S.D.)

Cl_F	Cl_S	ΣCl_I	Cl_E	Cl_E(ml/kg/min)
3.3	0.52	3.8	0.36	3.9
(1.4)	(0.22)	(1.4)	(0.09)	(0.6)

Discussion. While the present results are derived from blood samples obtained on a sampling schedule similar to that used by Homer and Stanski for the bolus portion of their study,[2] the results are consistent with those of Christensen et al.[1] There are several possible explanations for the inconsistency of these results. For example, Homer and and Stanski administered thiopental as a bolus to some patients and by an infusion lasting up to five minutes to others.[2] Smaller estimates of central volumes would have been obtained in the patients to whom the drug was given by infusion because during the infusion many samples were obtained immediately downstream from the site of drug administration. In addition, indocyanine green (ICG) data indicate the early samples used in the present study and that of Homer and Stanski[2] were obtained before the criterion of uniform mixing within the classical central volume was satisfied. This suggests that a closer examination of early thiopental distribution after IV bolus administration is in order. Such a study might include a simultaneously administered marker of intravascular mixing (e.g., ICG), very frequent early arterial blood sampling, and a model more complex than the traditional three compartment model.

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