Title: AGE AND INTRAVASCULAR MIXING DURING INDUCTION WITH THIOPENTAL

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Introduction. Studies seeking to explain the increased reactivity of the elderly to thiopental have correctly focused on age-related changes in the initial distribution of this drug.[1-3] However, differences in the rate of drug administration as well as in the times, frequencies, and sites of first blood sampling have contributed to the equivocal nature of these results. The purpose of the present study was to examine the influence of age on intravascular mixing, which contributes significantly to initial drug distribution.[4]

Methods. Institutionally approved written informed consent was obtained from the 21 ASA Physical Status I or II males who participated in this study. They were 20 to 79 years of age and 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. A standard dose of thiopental, 3 mg/kg IV, was used; to ensure successful 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. Indocyanine green (ICG), 0.5 mg/kg, was administered, over 15 sec, concomitantly with thiopental. Arterial blood samples were obtained at half minutes intervals from 1 to 5 minutes after the start of ICG administration and at one minute intervals thereafter to 16 minutes. Plasma ICG concentrations were measured using a spectrophotometric technique which has been shown to produce results identical to those obtained by high performance liquid chromatography (HPLC).[5] Plasma concentrations were converted to blood concentrations using the hematocrit. Blood volume was determined from the ICG B-phase data using the standard indicator dilution technique; this value was corrected for drug loss during distribution (i.e., mixing). The disposition of ICG was described with a three compartment open mammillary system using the CONSAM digital computer program. Central blood volume (heart and pulmonary circulation) was assumed to be 25% of the calculated blood volume and Vd_{SS} was constrained to equal the blood volume estimate. Elimination clearance was from the peripheral compartments. The sum of the intercompartmental clearances (ΣCl_I) was calculated as a potentially useful index of interindividual variation in mixing.[6] 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 ICG in the present study are summarized in Tables 1 and 2. There was no relationship between age and any of these variables except elimination clearance. This relationship is described by the following equations: Cl_E = -0.008 Age + 1.529 (r = -0.523, $P < 0.05$) for nonnormalized clearance and Cl_E/kg = -0.066 Age + 15.562 (r = -0.432, $P < 0.05$) for mass normalized clearance.

Table 1: Volumes of distribution of ICG (ml/kg) $\bar{x}$(S.D.)

V_C	V_F	V_S	Vd_{SS}
17.2	18.2	33.4	68.9
(2.7)	(9.0)	(9.5)	(10.9)

Table 2: Clearances of ICG (L/min) $\bar{x}$(S.D.)

Cl_F	Cl_S	ΣCl_I	Cl_E	Cl_E(ml/kg/min)
6.2	1.3	7.4	1.1	12
(2.2)	(0.5)	(2.2)	(0.3)	(3)

Discussion. Other investigators seeking to explain the increased reactivity of the elderly to thiopental in terms of early distribution of the drug have found no change,[1] decreased fast clearance (Cl_F),[2] and decreased central (initial) distribution volume (V_C)[3] in the elderly. The present study, using frequent early blood samples, sought to describe age-related changes in intravascular mixing following administration of a standard dose of thiopental to patients 20 to 79 years of age. The present results suggest that the increased reactivity of the elderly to thiopental is not the result of age-related changes in either intravascular volumes or flows. Since drug distribution occurs by mixing, flow, and diffusion,[4] the pharmacokinetic basis of the increased reactivity of the elderly may lie in the age-related changes in drug diffusion due, perhaps, to changes in the distribution of flow in the elderly, as suggested by the decreased elimination clearance of ICG with age.

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