The Pharmacokinetics of Thiopental in Pediatric Surgical Patients

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Thiopental pharmacokinetics and protein binding were determined in 24 pediatric surgical patients with normal hepatic and renal function, ranging in age from 5 months to 13 yr. These pharmacokinetic data were compared with those from 11 adult patients previously studied at our institution. All pediatric patients received a single intravenous bolus of thiopental, 4.0 ± 0.08 mg·kg⁻¹ (mean ± SD), while the adult patients received 6.0 ± 0.74 mg·kg⁻¹. Distribution phase kinetics and volume of distribution at steady state (Vdss) did not differ statistically between the two groups. The degree of serum protein binding of thiopental also was similar in pediatric and adult patients with free fractions of 13.2% ± 1.5% and 15.6% ± 1.3%, respectively. The two patient groups showed a marked difference in elimination half-time and clearance of thiopental. Total drug clearance was 6.6 ± 2.2 ml·kg⁻¹·min⁻¹ for pediatric patients and 3.1 ± 0.5 ml·kg⁻¹·min⁻¹ for adults (P < 0.001). The elimination half-time of 6.1 ± 3.3 hours found in pediatric patients was significantly shorter (P < 0.005) than that for adults, 12 ± 6 hours. Linear regression of the pediatric data failed to achieve significance (P = 0.00) for elimination half-time to increase with age, while clearance decreased (P < 0.001) with increasing age. The shorter elimination half-time seen in infants and children was due solely to greater hepatic clearance. Thus, recovery time after large or repeated doses may be more rapid for infants and children than for adults because of the higher clearance. (Key words: Age factors; pharmacokinetics. Anesthesia: pediatric. Anesthetics, intravenous: thiopental. Pharmacokinetics: distribution, metabolism; pediatrics.)

Several investigators have determined the pharmacokinetics of thiopental in adults, 1–3 yet there are no data regarding its disposition in pediatric patients. There are age-related changes in the amount and distribution of body water, blood volume, relative amounts of muscle and adipose tissue, regional blood flow, binding of drugs by plasma proteins, and hepatic and renal functions. 4–7 These factors may alter drug absorption, distribution, metabolism, and excretion.

Dose–response studies have shown that the dose of thiopental required for induction of surgical anesthesia in unanesthetized children is greater than that usually recommended for adults (5–6 mg·kg⁻¹ vs. 3–4 mg·kg⁻¹).8 The objective of our study was to determine whether there are age-related changes in thiopental kinetics that would account for the increased dose requirements of pediatric surgical patients. We compared pediatric patients with an adult control group from a previous study conducted at our institution. 3

Methods and Materials

Pediatric Pharmacokinetics

Sixteen patients were studied, ranging in age from 5 months to 13 yr, with a mean age (±SD) of 6 ± 4.7 yr. The weight range was 7–55 kg, with a mean of 23 ± 14 kg. The group included seven girls and nine boys. All patients were ASA I or II status, with normal hepatic and renal function. The patients were undergoing orthopedic, plastic, and general surgical procedures involving minimal blood loss. Informed consent was obtained from the parents or guardian of each patient. The study protocol was approved by the Stanford Human Studies Committee.

Premedication was selected by the anesthesiologists caring for the patient. Four patients were unanesthetized. Three patients received meperidine 1 mg·kg⁻¹ and atropine 0.02 mg·kg⁻¹ im; four patients received atropine 0.02 mg·kg⁻¹ im; five patients received diazepam 5 mg po. Premedications were given 30 to 60 min before induction of anesthesia.

After placement of an indwelling intravenous catheter, anesthesia was induced with an intravenous bolus of thiopental 4 mg·kg⁻¹ through a 25-gauge butterfly needle temporarily placed in the opposite arm. Ten patients required inhalational analgesia with 60–70% nitrous oxide in oxygen and halothane 0.5% to facilitate placement of the venous cannulae. Anesthesia was maintained with halothane 0.5–1.5% (inspired) and 60–70% nitrous oxide in oxygen. Maintenance fluid was 5% dextrose in 0.225% saline. Blood loss was replaced with normal saline or lactated Ringer's solution to maintain intravascular volume.

After injection of the thiopental bolus, 0.5–1.5-ml samples of venous blood were withdrawn from the indwelling cannula according to the following schedule: 2, 4, 6, 10, 15, 20, 30, 60, min and 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 h. The serum was separated and stored at −20°C.
ADULT PHARMACOKINETICS

The pharmacokinetics of thiopental in 11 unpremedicated healthy adult surgical patients were determined in a previous study at our institution.\(^5\) The ages of the patients ranged from 23 to 61 yr (mean 34 ± 11 yr). Each patient was given an intravenous bolus of 6.0 ± 0.74 mg · kg\(^{-1}\) of thiopental for induction of anesthesia. Maintenance of anesthesia was achieved with enflurane 1–2% (inspired) in 70% nitrous oxide. Samples of blood were withdrawn through a radial artery catheter at 0.5, 1, 2, 3, 5, 7, 10, 15, 20, 30, 45 min and at 1, 1.5, and 2 h. Subsequent venous samples were obtained at 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, and 24 h. The serum was separated and stored at –20°C.

PROTEIN BINDING

The plasma protein binding of thiopental was determined in 11 healthy pediatric surgical patients, ranging in age from 10 months to 11 yr (mean 5.1 ± 3 yr). The weight range was 12–40 kg (mean 21 ± 11 kg). Three of these patients also participated in the pediatric pharmacokinetic study. Premedication again was selected by the anesthesiologist caring for the patient. Three patients were unpremedicated. Four patients received atropine 0.02 mg · kg\(^{-1}\) im; three patients received meperidine 1.0 mg · kg\(^{-1}\) im plus atropine 0.02 mg · kg\(^{-1}\) im. One patient received diazepam 0.2 mg · kg\(^{-1}\) po. After placement of an indwelling intravenous catheter and before induction of anesthesia, a 5-ml sample of blood for protein binding studies was withdrawn from each patient.

Protein binding of thiopental was determined in the 11 adult surgical patients of the previous study described above, using arterial samples drawn during the first 15 min after induction.

ANALYTIC TECHNIQUES

Total serum thiopental concentrations were measured by a high-performance liquid chromatography assay\(^6\) sensitive to 100 ng · ml\(^{-1}\). The free (unbound) fraction of thiopental in adults and children was determined by ultrafiltration of serum samples.\(^3\)

DATA ANALYSIS

Serum thiopental concentration versus time data were fitted to biexponential and triexponential equations using an extended least-squares nonlinear regression program,§ Chi-square testing was used to select the statistically preferred model (two or three compartment) for each patient.\(^10\) From the polyexponential equation distribution and elimination half-times, volume of the central compartment (V\(_c\)), volume of distribution at steady state (V\(_{ds}\)), and clearance were calculated using standard formulae.\(^11\) The latter three parameters were calculated both according to body weight (kg) and body surface area (m\(^2\)). All results were expressed as mean ± standard deviation. Mean values for these parameters and for the per cent unbound thiopental were compared (using Student’s unpaired t test) with values obtained from the adult pharmacokinetic study. The original adult thiopental concentration versus time data were reanalyzed using extended least-squares nonlinear regression because the data previously had been analyzed using a fixed weighting value of 1/x\(^2\). The null hypothesis was rejected when P values were equal to or less than 0.05.

Linear regressions of elimination half-time, clearance, V\(_{ds}\), and V\(_c\) on age were performed for the 16 pediatric pharmacokinetic study patients. Clearance, V\(_{ds}\), and V\(_c\) were normalized for both weight and body surface area. For example, clearance expressed as ml · kg\(^{-1}\) · min\(^{-1}\) and as ml · m\(^{-2}\) · min\(^{-1}\) was regressed against age. V\(_{ds}\) and V\(_c\) were expressed as 1 · kg\(^{-1}\) and 1 · m\(^{-2}\). Two patients had markedly outlying data points (one patient for age vs. clearance, another patient for age vs. elimination half-time). These two data points were excluded from the regression analyses.

Results

Figure 1 shows a triexponential serum thiopental decay curve for a representative pediatric surgical patient.
and a similar curve for an adult patient. Comparison of the residual sum of squares obtained by two- and three-compartment models showed a statistical preference for a three-compartment model in 15 of 16 pediatric patients. The remainder were biexponential.

Pharmacokinetic data for the pediatric and adult patients are presented in Table 1. Distribution kinetics, $V_{dss}$, and $V_c$ did not differ statistically. The elimination half-time for thiopental in infants and children was about one-half the adult value. In addition, the clearance of thiopental was twice as great in infants and children as in adults.

Linear regression of the pediatric data did not achieve significance for the elimination half-time to increase ($P = 0.06$) with increasing age (Fig. 2). When clearance was normalized for body weight and expressed as $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, clearance was found to significantly decrease ($P < 0.001$) with increasing age in the pediatric patients (Fig. 3). The mean value (±SD) for clearance expressed as $\text{ml} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$ was 163 ± 45, with a range of 110–301. No relationship was found when clearance was normalized for body surface area and regression against age performed. Similarly, no relationship was found between age and $V_{dss}$ or $V_c$ in the pediatric patients.

The mean unbound fraction of thiopental was 13.2 ± 1.5% in infants and children, virtually the same as in adults 13.6 ± 1.3%. Linear regression showed no relationship between age and percent unbound thiopental in the pediatric patients.

**Discussion**

Pharmacokinetic studies of thiopental in healthy surgical patients$^1$–$^3$ demonstrate an initial rapid distribution phase averaging 2–4 min, followed by a slower distribution phase averaging 40–50 min. The subsequent elimination phase lasts much longer, with a half-life of many hours.

The effect of age on thiopental disposition has been studied in adults. Jung et al. determined the pharmacokinetics of thiopental in 22 adult female surgical patients (aged 25–83 yr) after induction of anesthesia with an intravenous bolus of the drug.$^{12}$ A significant positive correlation appeared between age and volume of distribution at steady state, but no relationship was seen between age and $V_c$ or clearance. Elimination half-time increased with age because of the increased volume of distribution. The unbound fraction of thiopental significantly increased with age also. In contrast to findings
in the Jung et al. adult study, our pediatric patients demonstrate no age-related changes for thiopental in either \(V_{ds}\) or \(V_e\). However, they do have an elimination half-time for thiopental which is about one-half the adult value (6.1 vs. 12 h). Since elimination half-time is directly proportional to the volume of distribution and inversely proportional to clearance, the 50% decrease in elimination half-time is solely due to a twofold increase in clearance. The hepatic extraction ratio (clearance/hepatic blood flow) for thiopental is approximately 0.2, a low value.\(^{13}\) Clearance of drugs with low hepatic extraction ratios is dependent upon the unbound drug fraction in plasma and the intrinsic hepatic microsomal enzyme activity.\(^{14}\) We have shown that the free thiopental fraction is similar for children and adults. Thus, the greater clearance of thiopental in pediatric patients must be due either to an absolute increase in hepatic microsomal enzyme activity or to an increased hepatic mass relative to body weight.\(^{15}\) These two mechanisms have been invoked previously to explain accelerated elimination of other drugs, including diazoxide, ethosuximide, and theophylline\(^{16,17}\) in children. Neonatal hepatic enzyme systems are immature or absent at birth but mature within a short time.\(^{6}\) Whether or not the systems become quantitatively more active during late infancy and childhood than during adulthood is not known. However, with growth and development, there is a change in relative hepatic size. The total liver mass constitutes 4% of fetal body weight, whereas the adult liver constitutes only 2%. Thus, infants and children possess 50–100% more hepatic mass for drug metabolism.\(^{15}\)

Our data reveal significant age-related changes in thiopental kinetics. Coté et al. determined that the induction dose requirement for thiopental in unpremedicated patients aged 5–15 yr is higher than that usually recommended for adults.\(^{8}\) We gave 4 ng·kg\(^{-1}\) rather than 5–6 ng·kg\(^{-1}\) are suggested by Coté et al. because we allowed the use of premedication and we wanted to study patients younger than 5 yr of age. Both pharmacokinetic and pharmaco-kinetic mechanisms provide possible explanations for increased dose requirements in children. Homer and Stanski have shown that the relationship between the plasma concentration of thiopental and drug-induced electroencephalographic activity does not change with age in adults aged 24–88 yr.\(^{18}\) However, their data cannot be extrapolated to pediatric patients. It is possible that infants and children have decreased CNS sensitivity to thiopental compared to adults. There are also kinetic mechanisms that could increase dose requirements: 1) Increased protein binding or a decrease in unbound (free) drug would increase dose requirements because of less free drug being available to produce a clinical effect. However, plasma protein binding for thiopental is similar for children and adults. 2) More rapid drug distribution from the central to peripheral compartments might increase induction dose requirements. We found no significant difference in rapid and slow distribution half-times between children and adults. However, a rigorous comparison cannot be made because the pediatric samples were venous blood but the adult samples were arterial. 3) More rapid elimination of drug is not likely to be important in the response to a single bolus. 4) An increase in the volume of the central compartment would result in a lower initial plasma (and presumably brain) concentration of drug from any given dose. Our data showed no statistically significant difference in \(V_c\) between pediatric and adult patients (0.4 l·kg\(^{-1}\) vs. 0.28 l·kg\(^{-1}\)).

Our results have important implications for the practice of pediatric anesthesia. The termination of the effect of a single dose of thiopental is dependent upon both metabolism and redistribution of drug to peripheral tissues.\(^{5}\) Children therefore may recover slightly faster than adults after small doses. With large or repeated doses, redistribution becomes progressively less effective and metabolism more important in lowering plasma (and brain) concentrations. Recovery time after larger doses may be more rapid in children because of the shorter elimination half-time.

Pediatric patients with normal hepatic and renal function treated with infusions of thiopental for control of intracranial hypertension or status epilepticus will have higher dose requirements than adults. The steady state concentration resulting from a given infusion rate is equal to that rate divided by the clearance. On average, children 5 months to 13 years of age require twice as much thiopental as do adults to maintain a given steady state plasma concentration when the dose is calculated in mg·kg\(^{-1}\)·min\(^{-1}\). A simpler method would be to calculate the thiopental dose in mg·m\(^{-2}\)·min\(^{-1}\), as this expression of clearance does not change with age.

Our youngest patients was 5 months of age. Therefore, it is important not to apply our results in administering anesthesia to neonates and infants in the first few months of life. Further investigation is required to determine the disposition of thiopental in this age group.

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