catheter placement and narcotic administration. While we do not advocate our methods to all institutions, EMS in the correct clinical setting may be an acceptable modality of pain relief for surgical patients in private or semi-private rooms.

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Thiopental Requirements for Induction of Anesthesia in Children

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There is a wide patient-to-patient variation in the thiopental dose required to induce anesthesia. Lower doses are needed in the aged than in younger adults.[1–3] There is some uncertainty concerning the doses required in children, however. Some authors have reported that children need more thiopental in relation to bodyweight than adults,[4,5] while others have observed no difference.[1,3] One possible explanation for the divergent findings may be that small children need higher doses of thiopental, whereas older children do not, *i.e.*, the situation may be similar to what has previously been reported for the minimum alveolar anesthetic concentration (MAC) for volatile anesthetics.[6,7] To investigate this, we measured the thiopental dose needed to induce anesthesia in children of different ages.

METHODS

One hundred unpremedicated children, ASA 1 and 2, scheduled for elective surgery, were divided into six groups according to age: 1–6 months; 6–12 months; 1–4 yr; 4–7 yr; 7–12 yr; and 12–16 yr. Some demographic data are shown in table 1. Surface area was calculated in all patients.[8] All patients were NPO for at least 4 h preoperatively. The study was approved by our local committee on human research.

Children more than 3 months of age were pretreated with a local anesthetic cream to alleviate pain during venous cannulation.[9] Nine of the 19 patients less than 3 months of age had their veins cannulated on the ward before transportation to the operating suite. The catheter (22- or 24-gauge) was inserted in a hand vein or in an antecubital vein. Children more than 6 months of age were accompanied by a parent during induction.

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TABLE 1. Demographic Data

Study Group	No. of Patients	Median Age	Weight (kg)	Height (cm)	Body Surface Area (m^2)
1–6 months	27	2.4 months (1.0–5.1)	5.3 ± 0.2	59 ± 1	0.28 ± 0.01
6–12 months	9	8.6 months (7.2–10.4)	9.3 ± 0.3	73 ± 1	0.42 ± 0.01
1–4 yr	17	2.1 yr (1.0–3.9)	13.1 ± 0.6	89 ± 2	0.56 ± 0.02
4–7 yr	13	5.7 yr (4.0–7.0)	19.9 ± 0.7	114 ± 2	0.80 ± 0.02
7–12 yr	20	8.7 yr (7.0–12.0)	29.8 ± 1.4	135 ± 2.5	1.08 ± 0.03
12–16 yr	14	13.8 yr (12.2–15.5)	47.1 ± 2.4	160 ± 2.9	1.46 ± 0.05

Data are means ± SE, when applicable. Figures within parenthesis indicate actual age distribution within each age group.

When possible, anesthesia was induced with the child calmly resting on the operation table or in the parent's arms. Monitoring was with ECG and blood pressure, but, in the younger children, the blood pressure cuff was usually only applied after induction of anesthesia. In 27 of the 36 infants, pulse oximetry was added immediately after induction. Atropine, 0.01 $mg \cdot kg^{-1}$ (minimum dose 0.1 mg) was given iv. Thiopental (2.5%) was then administered as a bolus injection over approximately 5 s, and the tubing was flushed with saline.

The dose of thiopental that induced anesthesia in 50% of the children (ED_{50}) in each age group was obtained by the "Up and Down Method".[10] The method has previously been used to assess halothane and isoflurane MAC in children.[7,11] The technique requires that each patient can be classified as responder or nonresponder, *i.e.*, as asleep or not asleep. This was done on the basis of the reactions obtained when testing the lid reflex and placing the anesthesia mask on the child's face. The first patient in each group was given 5 $mg \cdot kg^{-1}$ of thiopental, and the lid reflex was tested 40 s after injection by gently brushing the upper and lower eye lash with a finger tip. If the patient blinked in response to the stimulus or moved so that the lid reflex could not be assessed, he/she was considered to be "not asleep" and further thiopental was given as needed. If a negative lid reflex was obtained, the patient's acceptance of the anesthesia mask was tested by gently placing the mask on the face and moving the chin to the sniffing position. No attempts were made to control ventilation. The response during this maneuver and during the next 30 s while breathing oxygen was observed. The patient was classified as "not asleep" if there was coughing or gross movements, *i.e.*, if the patient moved head or trunk or if an elbow or foot was lifted from the table. Small movements of the hands or feet were accepted. The observations were made by an anesthetist who was unaware of the administered thiopental dose. The dose selected for the subsequent patient in each age group was based on the response observed in the preceding patient (*i.e.*, if the preceding patient had a positive lid reflex 40 s after injection or moved during the subsequent 30 s of oxygen breathing, the thiopental dose for the next patient was increased by 1 $mg \cdot kg^{-1}$; if no such reaction was observed, the thiopental dose was decreased by 1 $mg \cdot kg^{-1}$). After the 70 s study period, general anesthesia was established with one of the potent inhaled anesthetics, either *via* a mask or after tracheal intubation using succinylcholine.

ED_{50} was calculated as described by Dixon,[10] *i.e.*, essentially as the mean thiopental dose in each age group. To determine the standard error of the estimated ED_{50} in the age group, consecutively studied patients were divided into subgroups with a "nominal sample size"§ of 2 and ED_{50} for the subgroups was assessed. The standard error was calculated from the variation of the ED_{50} values of the subgroups. The differences between groups were analyzed by one-way analysis of variance (treating each subgroup as one observation) and Newman-Keuls test. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Seventy-four children had a negative lid reflex 40 s after thiopental administration. Forty-eight (65%) of

§ The nominal sample size is a count of the number of patients, beginning with the first pair of patients with unlike responses. A run of, *e.g.*, asleep-asleep-awake has a nominal sample size of 2.[10]

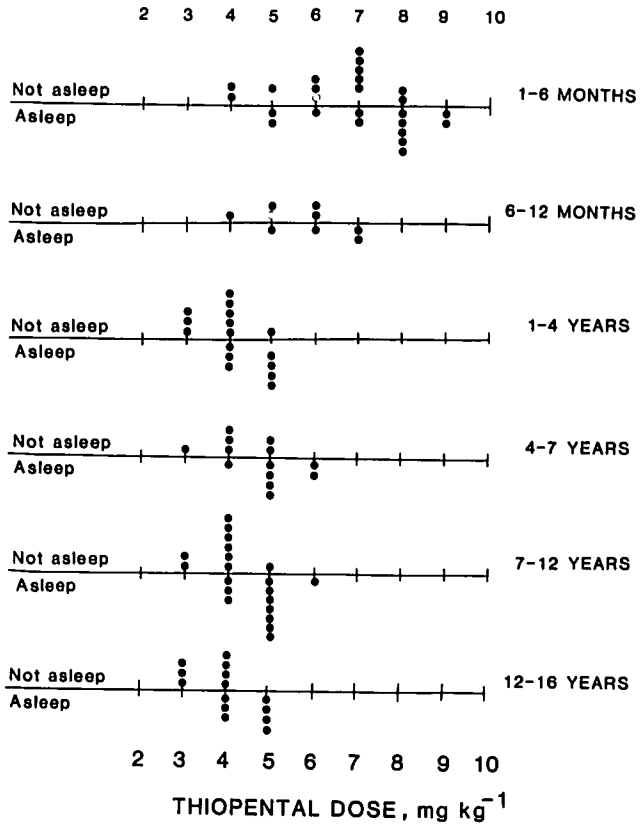

FIG. 1. Data for an individual patient are given as a circle. The patients studied before the first pair of patients with unlike responses are indicated by open circles. The position of the circle along the horizontal line indicates the administered thiopental dose. The position of the circle below or above the line indicates whether the patient fell asleep or not, respectively.

these subsequently accepted the anesthesia mask and were hence classified as asleep. Figure 1 shows the responses at different induction doses. The corresponding ED_{50} values in the six age groups are given in figure

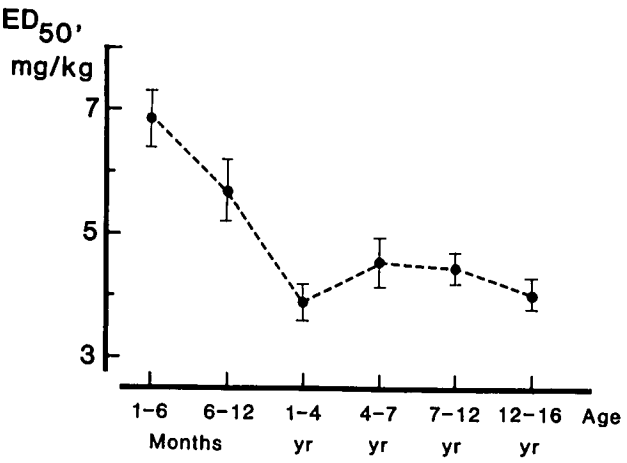

FIG. 2. Estimated $ED_{50} \pm SE$ in the various age groups.

2. ED_{50} in the youngest age group was greater than ED_{50} in children 1–16 yr of age ($P < 0.01$ for all comparisons). ED_{50} in infants 6–12 months of age was significantly greater than ED_{50} in children 1–4 yr ($P < 0.05$), 7–12 yr ($P < 0.05$), and 12–16 yr ($P < 0.01$).

One patient in the oldest age group, given 4 $mg \cdot kg^{-1}$, coughed when the mask was applied and developed laryngospasm which necessitated additional thiopental and oxygen ventilation. Otherwise, no incident of hypoxia, bradycardia, or clinically significant hypotension was observed, although brief periods of irregular breathing and breath-holding were commonly noted.

DISCUSSION

Many different reactions may be used to assess the depth of anesthesia. In our study, the lid reflex and the response when applying the mask to the face were chosen because these criteria are commonly used in clinical practice. Both responses signify light planes of anesthesia.[4,12] We selected the bolus technique because this was the easiest way to control the rate of administration which is known to affect thiopental requirements.[13,14] The initial dose of 5 $mg \cdot kg^{-1}$ was chosen because previous tests indicated that this dose could be used safely and would be close to ED_{50}. The lid reflex was tested 40 s after thiopental administration, and acceptance of the anesthesia mask immediately thereafter. The subsequent 30 s of accepting the mask was regarded as a minimum requirement for satisfactory anesthesia induction. Coté *et al.* found some variability in these responses 30 s after thiopental injection in children 5–15 yr of age, while the responses at 60 and 90 s were more consistent.[4] Because of the younger patients included in the present study, we selected a somewhat earlier time for testing the responses. Infants have a shorter arm-brain circulation time than older subjects, and it is conceivable that 40 s was adequate for thiopental to take its effect only in the infants. If so, we may have underestimated the true difference in thiopental requirements between the younger and the older age groups.

We have not found any previous reports of dose requirements in children related to age. In unpremedicated children 5–15 yr of age, Coté *et al.* found that ED_{50} for loss of the lid reflex and for acceptance of the anesthesia mask 60 s after a thiopental bolus was 2.9 and 3.4 $mg \cdot kg^{-1}$, respectively.[4] The greater dose observed by us in corresponding age groups may be due to the fact that Coté *et al.* determined ED_{50} for loss of each response separately, whereas we determined the dose needed to abolish the lid reflex at 40 s, and to keep the patient from moving or coughing while placing the anesthesia mask and for 30 s thereafter. Duncan *et al.*,[5] on the other hand, found that ED_{50} for abolishing the lid

reflex in children 1–12 yr of age was 5–6 mg·kg^{-1}, *i.e.*, somewhat greater than in the present study. However, in that study, thiopental was administered until the lid reflex was abolished and not as a single bolus.

There are several possible explanations for the differences in dose requirements in infants and older children found in the present study. First, there may be a difference in "early" distribution kinetics. Sorbo *et al.*[15] found no difference in thiopental plasma protein binding, in distribution kinetics, or in volume of distribution at steady state (VD_{ss}) between children and adults. However, after bolus injection, thiopental reaches its target organ and exerts its effect before a steady state is reached. Their findings, therefore, do not exclude age-related differences in the arterial blood concentration curve.[2] Such differences are, in fact, to be expected simply because of the greater cardiac output in relation to bodyweight in infants. This should result in a lower first-pass thiopental concentration in the blood perfusing the brain in infants than in older children. Cardiac output is closely correlated to the body surface area of the child,[16] and one would, therefore, expect a similar ED_{50} (mg·m^{-2}) in infants and children. Since we used the Up-and-Down technique, our figures cannot be directly translated into ED_{50} (mg·m^{-2}). If the thiopental dose per m^2 body surface area is calculated in each age group, however, this gives 127 ± 6 and 131 ± 6 mg·m^{-2} (mean ± SEM) in the youngest and oldest age group, respectively. The requirements in the intermediate ages would be less, however, with a minimum of 96 ± 4 mg·m^{-2} in children 1–4 yr of age.

Other possible explanations for the different requirements in infants and children include slower equilibration between plasma and brain in infants, and differences in pharmacodynamics. The former explanation cannot be excluded but seems less likely, since blood:brain equilibrium occurs relatively rapidly, both in young adults and in the elderly.[2] A difference in CNS sensitivity between infants and children seems more plausible. There is a similarity between the pattern for halothane and isoflurane MAC in children of various ages[6,7] and our data (fig. 2). Furthermore, preliminary studies in a few neonates suggest that these need less thiopental than older infants, which is consistent with the reduced MAC reported in this age group.[7,11] Different mechanisms are probably involved, however, since thiopental induces sleep at similar plasma concentrations in the young adult and in the elderly,[2] while MAC for halothane changes with age.[6] The great variation in thiopental requirements in the youngest age group (fig. 1) might be explained by the marked changes in body composition and CNS maturation which occur during the first 6 months of age.

Our data confirm previous findings that children generally need more thiopental than adults.[4,5] ED_{50} in children above 1 yr varied between 4–5 mg·kg^{-1}. Hence, we agree with Coté *et al.* that the bolus dose needed for fast and reliable induction in healthy children is 5–6 mg·kg^{-1}.[4] In infants, 7–8 mg·kg^{-1} is usually required. We observed no adverse cardiovascular effects in the present study, but we did not study this systematically. The possibility of a lower dose requirement in neonates should be noted.

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