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Methohexital Dissolved in Lipid Emulsion for Intravenous Induction of Anesthesia in Infants and Children

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The induction dose of thiopental and propofol has been shown previously to vary during childhood. The methohexital dose needed for satisfactory induction of anesthesia in 50% of patients (ED_{50}) was determined in 75 infants and children, 1 month to 16 yr of age. An intravenous bolus of methohexital, dissolved in a lipid emulsion to decrease pain on injection, was given over 10 s. After 30 s the anesthesia mask was applied. The patient was considered to be asleep if there were no gross movements when the head was placed in the sniffing position and the anesthesia mask applied, and no response to verbal command (tested in children more than 4 yr of age) during the next 30 s while the patient breathed O_2. ED_{50} (± SE) was 2.6 ± 0.2 mg/kg in infants 1–6 months of age, 1.9 ± 0.1 mg/kg in infants 7–11 months of age, 1.4 ± 0.1 mg/kg in children 1–3 yr of age, 1.1 ± 0.1 mg/kg in children 4–7 yr of age, and 1.3 ± 0.1 mg/kg in children 8–16 yr of age. ED_{50} in each of the two groups of infants was significantly greater than ED_{50} in each of the three other groups ($P < 0.05$). Pain or discomfort on injection was observed in 1 infant and 3 children (5%). Eight patients (11%) had apnea longer than 15 s, and excitatory phenomena occurred in 9 (12%). It is concluded that the dose of methohexital needed for induction of anesthesia varies with age. Infants less than 6 months of age required almost twice as much as older children in relation to body weight. Pain on injection was infrequent with methohexital dissolved in a lipid emulsion. (Key words: Anesthesia: pediatric. Anesthetics, intravenous: methohexital.)

ALTHOUGH SHORT-ACTING and associated with rapid recovery after short procedures, methohexital is less popular than thiopental for intravenous induction.[1,2] One reason is the pain commonly associated with injection of methohexital in small diameter veins.[3,4] In adults we found that dissolving the drug in a lipid emulsion (Intralipid®) almost abolished injection pain but did not affect potency.[5] The intravenous induction dose of thiopental and propofol has been shown previously to vary during childhood.[6,7] The aim of the present study was to assess the dose requirements of the methohexital–lipid solution in infants and children of different ages.

Materials and Methods

Seventy-five children scheduled for elective surgery were divided into five groups according to age: 1–6 months, 7–11 months, 1–3 yr, 4–7 yr, and 8–16 yr (table 1). All were ASA physical status 1 or 2 and had been born full-term (> 37 weeks gestational age) with a birth weight greater than 2,500 g. Children with allergies to egg or soybean or with signs of upper airway infection or fever were excluded, as were those in whom venous access was not readily achieved. Typical procedures included hernia repair and circumcision. The children were studied after approval by the local Human Studies Committee and after obtaining informed consent from the parents.

The patients had fasted at least 4 h before induction of anesthesia. After treatment with a local anesthetic ointment (EMLA®, Astra Pharmaceuticals) a 24-G catheter was placed in a vein in the hand, the antecubital fossa, or, in one case, the foot. According to departmental routine, infants received intravenous atropine 0.02 mg/kg (minimum dose 0.1 mg) immediately before induction, whereas children greater than 1 yr of age were given rectal atropine 0.02 mg/kg (maximum dose 1.0 mg) 20 min before induction of anesthesia. No opioids or hypnotics were given before induction of anesthesia. Monitoring included ECG, blood pressure, and hemoglobin O_2 saturation with pulse oximetry (Sp_{O_2}). Patients greater than 6 months of age were accompanied by a parent during induction.

In infants 1–12 months of age, O_2 was flushed over the face for 1 min before methohexital administration. Children older than 12 months did not breathe O_2 prior to induction. Anesthesia was induced with a precalculated dose of 1% methohexital in a lipid emulsion.[5] The solution, which had been prepared by mixing 500 mg sodium methohexital dissolved in 5 ml of saline with 45 ml lipid emulsion (Intralipid®, Kabi Pharmacia Pharmaceuticals) within 2 h of induction, was administered as an intravenous bolus over approximately 10 s through a three-way stopcock and was flushed in with 4 ml saline.

The methohexital dose needed for satisfactory induction of anesthesia in 50% of patients (ED_{50}) was obtained by the "up-and-down" method.[8] The procedure was as follows. The first patient in each age group was given 1.4 mg/kg methohexital. Thirty seconds after injection, the lid reflex was tested. The response was recorded but not used for the subsequent classification of induction as satisfactory or unsatisfactory (see Discussion). The chin was gently moved into the sniffing position and the anesthesia mask placed over the face. The response to verbal command ("open your eyes") also was recorded in children

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TABLE 1. Patients

Study Group	n	Age	Weight (kg)	Length (cm)
1–6 months	20	3.0 ± 0.3 months (1.4–6.9)	5.9 ± 0.3 (3.2–8.8)	60 ± 1 (49–70)
7–11 months	15	8.2 ± 0.8 months (7.0–11.8)	8.6 ± 0.3 (6.5 ± 11.5)	71 ± 1 (66–79)
1–3 yr	13	2.6 ± 0.3 yr (1.0–3.9)	13.8 ± 0.9 (8.7–21.5)	91 ± 4 (69–112)
4–7 yr	15	5.7 ± 0.3 yr (4.1–7.8)	21.4 ± 1.2 (17.5–32.5)	117 ± 2 (105–134)
8–16 yr	12	11.7 ± 0.9 yr (8.1–15.8)	41.9 ± 4.2 (22.5–63)	153 ± 5 (127–183)

Figures are given as mean ± SE (range).

older than 4 yr when the chin was lifted and while the anesthesia mask was held. The responses during the following 30 s, while the child breathed O_2 through the mask, were assessed by an observer unaware of the administered dose. If the child moved the head or trunk or lifted an elbow or a foot from the table ("gross movements"), opened eyes on command, or coughed, induction was classified as unsatisfactory and additional methohexital was given as needed. The dose chosen for the next patient in that age group was then increased. Conversely, if no response or only minor movement of a hand or a foot was observed, induction was classified as satisfactory and the methohexital dose for the next patient in the group was decreased. The doses were spaced evenly on a logarithmic scale (fig. 1) with an interval of $10^{0.05}$; *i.e.*, the current dose was either greater or less than the preceding dose by a factor of 1.12. After the 60-s study period, general anesthesia was established with halothane or isoflurane in N_2O and O_2, either *via* mask or after tracheal intubation using succinylcholine.

Systolic blood pressure, heart rate, and Sp_{O_2} were recorded just before and 1 min after the methohexital bolus. The blood pressure was measured with an inflatable cuff and a mercury manometer, using a pulse oximeter (Nellcor N-100) as pulse indicator.[9] Pain or discomfort on injection, as indicated by withdrawal of the extremity, crying, or verbal comment, was noted, as was excitatory phenomena such as hiccups or muscle twitches in the face, arms, or legs. Apnea, as indicated by absence of chest wall movement and anesthesia bag movement, lasting longer than 15 s also was recorded.

ED_{50} was calculated as described by Dixon.[8] The method allows estimation of ED_{50} from a relatively small sample size and has been used to determine MAC for inhalational anesthetics.[10,11] To determine the standard error (SE) of ED_{50} in each group, ED_{50} was determined in subgroups of consecutively studied patients, each with a "nominal sample size" of two.[8] (The nominal sample size is the number of patients, beginning with the first pair of patients with unlike responses. A sequence of responses of, for example, unsatisfactory–unsatisfactory–satisfactory has a nominal sample size of two). Differences between *age* groups were analyzed by one-way analysis of variance (ANOVA) (treating each subgroup as one observation). If ANOVA rejected the null hypothesis that children of all ages needed the same dose (milligrams per kilogram), the analysis was completed by the *t* test for unpaired data to assess the significance of differences between age groups. The data were also submitted to logistic regression analysis. Changes in heart rate and blood pressure within groups were assessed by the two-sided *t* test for paired data. $P < 0.05$ was considered to indicate statistical significance.

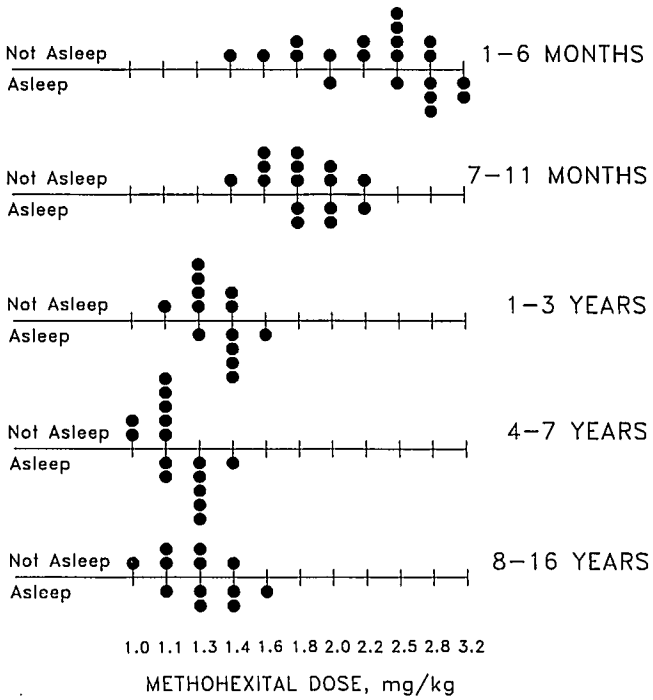

FIG. 1. Results of injection of different doses of methohexital. Each filled circle represents one patient. The position of the circle below or above the line indicates whether induction was classified as satisfactory or not.

TABLE 2. Heart Rate and Blood Pressure During Induction of Anesthesia

Study Group	n	Methohexital Dose (mg/kg)	Systolic Blood Pressure (mmHg)		Heart Rate (beats/min)	
			Before Induction	1 min after Induction	Before Induction	1 min after Induction
1–6 months	19	3.2 ± 0.1	85 ± 3	96 ± 4*	155 ± 6	190 ± 4†
7–11 months	13	2.7 ± 0.2	91 ± 3	108 ± 6*	126 ± 5	169 ± 4†
1–3 yr	13	1.6 ± 0.1	102 ± 3	114 ± 3†	106 ± 4	128 ± 4†
4–7 yr	15	1.6 ± 0.1	103 ± 2	107 ± 3	89 ± 5	115 ± 6†
8–16 yr	12	1.6 ± 0.1	113 ± 6	118 ± 4	84 ± 5	112 ± 5†

Means ± SE. The methohexital dose includes supplementary doses given to children who did not fall asleep after the initial doses. Significant changes in relation to the value before induction is shown. Note that infants (0–1 yr) were given intravenous atropine immediately before induction.

* $P < 0.05$.

† $P < 0.01$.

Results

Forty-three patients moved in response to the anesthesia mask and were given additional methohexital. None of the remaining patients coughed or opened eyes on command, and these 32 were therefore classified as asleep. Of these patients, the lid reflex was present in 4 and could not be tested because of minor periorbital muscle twitching in 1. Of the 43 patients classified as not asleep, the lid reflex was absent in 14 and could not be assessed in 12 because of minor periorbital muscle twitching (n = 4) or gross movements (n = 8).

ED_{50} (mean ± SE) was 2.6 ± 0.2 mg/kg in infants 1–6 months of age, 1.9 ± 0.1 mg/kg in infants 7–11 months of age, 1.4 ± 0.1 mg/kg in children 1–3 yr of age, 1.1 ± 0.1 mg/kg in children 4–7 yr of age, and 1.3 ± 0.1 mg/kg in children 8–16 yr of age. Individual responses are shown in figure 1. There was a significant difference in ED_{50} between infants 1–6 months and the four other groups ($P < 0.05$ for the comparison to infants 7–11 months and $P < 0.001$ for each of the other three comparisons). Also, there was a significant difference in ED_{50} between infants 7–11 months and the three older age groups ($P < 0.001$ for each comparison). There was no significant difference in ED_{50} between the 1–3 yr, 4–7 yr, and the 8–16 yr age groups. ED_{50} values for the different age groups obtained by logistic regression analysis were within 0.1 mg/kg of the values obtained with the method described by Dixon.[8]

Results of blood pressure and heart rate measurements 1 min after injection are shown in table 2. Movements prohibited blood pressure measurements in three patients. Systolic blood pressure decreased by more than 20% of preinduction value in one infant (from 80 to 60 mmHg) and in one 8-yr-old child (from 160 to 110 mmHg). There were no significant changes in blood pressure in the older age groups, but a 15% mean increase was observed in children less than 4 yr of age ($P < 0.05$ for each age group). Heart rate increased in all patients, except in one infant in whom it decreased by 5 beats per min. No clinically significant changes in heart rate or blood pressure were observed after the 1-min study period, during transition to maintenance anesthesia.

The occurrence of adverse effects is shown in table 3. One infant, in whom the intravenous catheter was placed in a vein in the foot, cried, and three children complained of discomfort during injection. Apnea lasting longer than 15 s occurred in two infants and seven children. Of these, one infant and one child were given ventilatory assistance because of prolonged apnea (> 40 s) and because of a decrease in Sp_{O_2} to less than 95%, respectively. Hiccups occurred in two, and minor muscle twitches were observed in seven patients.

Discussion

The criteria used for satisfactory induction—no movement or coughing when the anesthesia mask was placed over the face or during the following 30 s—were chosen because previous studies had shown that this endpoint can be assessed easily and usually signifies a plane of anesthesia that allows smooth transition to maintenance anesthesia.[6,12] The response to verbal command was tested because of the possibility that older children might accept the anesthesia mask though awake. Absence of the lid reflex was not used as a criterion because experience in adult patients indicated that it would be difficult to eval-

TABLE 3. Some Observations during Induction of Anesthesia with Intravenous Methohexital

Age Group	Discomfort or Pain on Injection	Apnea (>15 s)	Hiccups or Muscle Twitches
1–6 months	1	2	3
7–11 months	0	0	2
1–3 yr	1	2	1
4–7 yr	1	1	1
8–16 yr	1	3	2
All patients	4/75 (5%)	8/75 (11%)	9/75 (12%)

uate, partly because methohexital sometimes causes muscle twitches around the eyes.[5,13] The high incidence of absent lid reflexes in children classified as not satisfactorily induced agrees with previous studies[13] and suggests that the lid reflex is not clinically useful when assessing anesthetic depth during methohexital induction.

Although there are no comparable data describing methohexital requirements for intravenous induction in infants, the ED_{50} values obtained in children greater than 1 yr of age in the present study are similar to those found in adults[5] and are consistent with the 1.1–1.2-mg/kg "minimum sleep dose" reported by Keep and Manford[14] in 2–16-yr-old children. One reason for the observed difference in dose requirements between infants and children could be that infants have higher neuronal density than children.[15] Also, blood volume and the size of the vessel-rich compartment are greater in infants,[16] as is cardiac output in relation to body weight.[17] Infants can therefore be expected to have lower peak concentrations in the blood perfusing the brain after a bolus injection than older children.[16,17] A greater dose requirement in infants than for children has been reported also for thiopental[6] and propofol,[7] for which the ratios of ED_{50} in infants 1–6 months to that in children older than 7 yr were 1.6 and 1.25, respectively. Several of the patients in the present study who were classified as "not asleep" only moved toward the end of the 30 s + 30 s observation period. Also, some patients who were classified as "asleep" moved shortly afterward. The author's experience during a previous study of propofol[7] with a similar investigation protocol as in the current study was that a child who did not initially respond to the face mask remained immobile until the transition to maintenance anesthesia. This is consistent with the finding in adults that the time to eye-opening after intravenous injection is longer for propofol than for either methohexital or thiopental,[18] and the recent observation in adults that the deep-anesthesia phase, assessed with EEG, lasts longer after a single intravenous injection of propofol than after methohexital.†

Only one patient indicated marked pain in response to methohexital–lipid injection. This is in contrast to the high incidence of moderate to severe pain on injection of aqueous methohexital into small veins[3,4] and confirms that dissolving methohexital in lipid emulsion decreases pain on injection.[5] The other side effects noted during induction are in agreement with previous studies. Apnea lasting longer than 30 s has been reported in 15% of adults[1,2] and in three of nine children 6–15 yr of age.‡ The mild excitatory phenomena that occurred in nine patients did not affect the categorization of the child as "asleep" or "not asleep."

Despite the rather great methohexital doses administered—12 infants were given doses of 2.5 mg/kg or more—no adverse cardiovascular effects were observed in these otherwise healthy patients. It should be noted that pretreatment with atropine probably affected the changes in heart rate and blood pressure especially in infants, in whom atropine was given intravenously. An increase in heart rate with methohexital injection has been documented previously in adult patients not premedicated with atropine.[2,4,19,20]

In conclusion, ED_{50} for satisfactory induction of anesthesia with methohexital varied considerably with the age of child. The dose requirement in infants 1–6 months of age was about twice that of children 8–16 yr of age. Intravenous methohexital dissolved in a lipid emulsion may be a useful alternative to thiopental and to propofol.

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