Anesthesiology
62:567–570, 1985

Methohexital Plasma Concentrations in Children Following Rectal Administration

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Despite the increasing use of rectal methohexital as a premedicant–induction agent in pediatric anesthesia, there are no data to confirm the assumption that low plasma methohexital concentrations are the cause of inadequate sedation of children and that high concentrations are associated with the loss of consciousness. Plasma methohexital concentrations were determined in 20 ASA Class I children, ages 2–7 yr, after the rectal administration of methohexital (25 mg/kg). Seventeen of the 20 children in this study fell asleep after receiving the drug and achieved peak plasma concentrations greater than 2 μg/ml. The maximum plasma methohexital concentration in children that did not fall asleep was less than 2 μg/ml. The mean time to the onset of sleep after drug administration was 8.3 min (at which time the mean plasma concentration was 4.4 μg/ml). The mean peak plasma concentration and the mean time to peak plasma concentration were 4.7 μg/ml and 13.9 min, respectively. Loss of consciousness after rectal administration of methohexital correlates well with the plasma concentration of the drug. (Key words: Anesthesia: pediatric. Pharmacokinetics: methohexital. Premedication, rectal: methohexital.)

METHOHEXITAL has been administered rectally to pediatric patients as a preanesthetic drug for more than two decades. Since the initial reports,[1,2] the recommended dose has been increased at least twofold. Rectally administered methohexital induces sleep in 84 to 93% of patients within 15 min after a single dose of between 20 and 30 mg/kg.[3] Occasionally, however, a patient will not fall asleep even after 30 min have elapsed or after three repeated doses of the drug have been administered. To evaluate the wide variation of response to 25 mg/kg, concentrations of methohexital in plasma were determined after rectal administration of the drug and correlated with the state of consciousness of each child.

Methods

Twenty healthy ASA Class I children scheduled for elective surgical procedures were studied. The children ranged in age from 2 to 7 yr (4.4 ± 1.7 yr; mean ± SD) and weighed 11.8–22.8 kg (16.4 ± 3.5 kg). None of the children had enemas preoperatively. The protocol for this study was approved by the Subcommittee on Human Studies, Committee on Research of our institution, and written parental consent was obtained.

Methohexital was prepared for each patient by dissolving 500 mg sodium methohexital crystals in 5 ml of sterile water to form a 10% solution. This 10% methohexital solution was drawn into a 6-ml syringe. A 14 Fr Argyle® oxygen catheter was cut approximately 7 cm from the tip and attached to the syringe. After lubricating the catheter, a dose of 25 mg/kg of methohexital was administered rectally to each patient. The time lapse from the administration of the drug to the onset of sleep was recorded. The onset of sleep was defined as loss of consciousness, unresponsiveness to verbal stimulation, and absence of voluntary and purposeful movements when unstimulated.

When possible, a 22-gauge Jelco® catheter was placed in a vein in the back of the patient's hand prior to methohexital administration. Venous blood samples (1.9–2.0 ml) were drawn through this catheter prior to and at 5, 10, 15, 30, 45, 60, and 120 min after the drug was given. An additional sample was drawn immediately after the onset of sleep in nine patients. In four children, a catheter could not be placed before they were asleep without causing undue psychologic trauma to them or to their parents. In those cases, blood samples were not obtained until after the patient fell asleep. In very small children, blood was not taken at every sample time in order not to exceed the guidelines (1 ml/kg of body weight) of our institution for the volume of blood that

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Received from the Anesthesia Services of the Massachusetts General Hospital and the Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts, Departments of Medicine and Pharmacology, Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts, and the Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Accepted for publication November 7, 1984. Dr. Gaudreault was supported by a grant from L'Institut de Recherche en Santé et en Sécurité de Travail du Québec.

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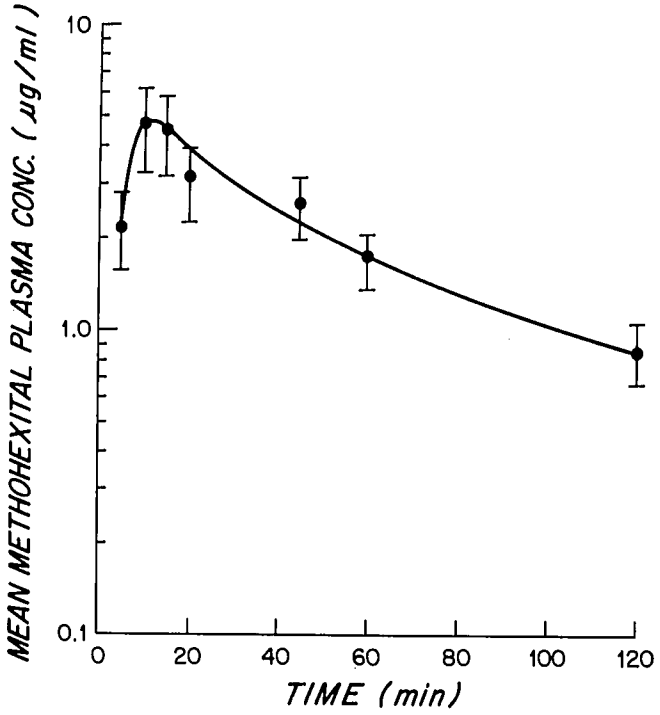

FIG. 1. Mean plasma methohexital concentration time curve after rectal administration of 25 mg/kg. The values represent the mean ± SE.

may be drawn from children that participate in human studies. The priority for eliminating samples was the premethohexital sample first, then the 4 min sample, and finally the onset of sleep sample.

Within 5 min following the onset of sleep, patients were anesthetized by face mask with halothane, nitrous oxide, and oxygen. Those children that did not fall asleep within 30 min after methohexital administration received no additional medication. They were taken to the operating room and anesthetized via a face mask with halothane, nitrous oxide, and oxygen.

High-pressure liquid chromatography was utilized to analyze the methohexital concentration in the plasma samples. Methohexital was extracted from the patient's plasma samples by mixing 5 ml petroleum ether:N-amyl-alcohol (100:2) with 0.5 ml of plasma for 60 s. After centrifugation, the organic solvent layer was transferred to a conical tube and evaporated to dryness under a stream of nitrogen. The sample then was reconstituted with 150 μl of acetonitrile and water (60:40). Fifty microliters of this solution was injected into a Waters uBondapak C-18® column (Waters Associates Inc., Milford, Massachusetts 01757). The flow rate was 90 ml/h. The data were obtained with a Waters® absorbance detector Model 441 at a wave length of 214 nm and recorded on a Waters Data Module 730®. Pooled plasma from volunteers on no medication was used for control plasma. The concentrations of methohexital in plasma were calculated from calibration graphs derived from control plasma to which known amounts of methohexital had been added. The efficiency of extraction from control plasma of known concentrations of methohexital was evaluated over the concentration range 0.1–20 μg/ml. At 0.1 μg/ml, recovery of the drug was 80 ± 10%, while at 20 μg/ml recovery was 78 ± 2%. On each day that samples were measured, a calibration graph was obtained; these graphs were identical ± ≤10%. All samples were run in duplicate. The sensitivity of the assay was 10 ng/ml.

Results

Seventeen of the 20 patients studied fell asleep after receiving methohexital. The time from the administration of the drug to the onset of sleep in these 17 patients was 8.3 ± 3.6 min (mean ± SD) (range 5–18 min). Mean methohexital plasma concentrations in the children that fell asleep are shown in figure 1. The mean ± SD methohexital concentration of the plasma samples obtained from nine patients at the onset of sleep was 4.3 ± 2.4 μg/ml (range 0.7–7.2 μg/ml). The plasma methohexital concentration in eight of these patients was greater than 2 μg/ml. Three other patients that did not have plasma samples drawn when sleep commenced had plasma methohexital concentrations before and after the onset of sleep of 0.3 and 3.0, 0.5 and 2.5, and 2.0 and 3.5 μg/ml, respectively. Five additional children slept before the first plasma sample could be obtained. In each of these patients, the methohexital concentration in the initial plasma sample was greater than 2 μg/ml.

Figure 2 shows the plasma methohexital concentrations in the patients with the highest and the patients with the lowest peak concentrations in the group that fell asleep and in the group that remained awake. All the patients that fell asleep had peak plasma levels above 2 μg/ml, whereas those that remained awake had peak levels below 2 μg/ml (fig. 2). The peak plasma methohexital concentration in the children that fell asleep was 5.3 ± 0.5 μg/ml (range 2.5–9.3 μg/ml). The time interval from the administration of methohexital to the highest measured plasma concentration in these children was 14.9 ± 2.0 min (range 5–30 min).

Three patients in this study defecated after receiving methohexital. Two defecated after falling asleep. Their peak methohexital plasma concentrations were 3.5 and 8.9 μg/ml. The third child did not fall asleep. She defecated approximately 8 min after the drug was administered. The peak methohexital concentration measured in her plasma samples was 0.9 μg/ml.

In the children that fell asleep, the plasma methohexital concentration was greater than 2 μg/ml in 100%, 75%, 69%, 47%, and 12% of the duplicate plasma samples obtained 15, 30, 45, 60, and 120 min, respec-

tively, after drug administration. Methohexital was present in the plasma 60 min after methohexital administration in all patients that fell asleep but was not detected with this assay in the 120-min plasma samples from four of these same patients. In all three patients who failed to sleep, methohexital was detectable at 15 min; in two of these patients, the drug could not be detected at 30, 60, and 120 min.

Discussion

Methohexital has been administered rectally as a premedicant–induction agent to more than 12,000 children in our institution. In an early study, we reported that 84% of the patients that received 25 mg/kg of methohexital fell asleep within 15 min.[3] The sleep induction time of this group was 7.2 ± 2.3 min (mean ± SD). In this present study, 17 (85%) of the 20 patients receiving methohexital (25 mg/kg) fell asleep. All children that fell asleep did so within 15 min (except for one who fell asleep at 18 min), and the mean (±SD) sleep induction time was 8.3 ± 3.6 min. There were no statistically significant differences between the two studies.

Our results suggest that a given patient is likely to fall asleep if the peak plasma methohexital concentration achieved exceeds 2 μg/ml (fig. 2). The susceptibility of each patient to sleep as defined in this study may be altered by factors such as sleep deprivation, anxiety, agitation, pain, drug sensitivity, and the bioavailability of the administered drug. These factors may explain the variation in the methohexital concentration at the onset of sleep in the patients that we studied.

Approximately 50 min after rectal administration of methohexital, the mean plasma level dropped below 2 μg/ml (fig. 1). However, the variability in the rate of decrease in the plasma concentration may account for the prolonged recovery time of some children after short anesthetics, as suggested by the fact that several children had >2 μg/ml of methohexital in their 60- and 120-min plasma samples.

The wide variation in plasma methohexital concentrations in our patients can be attributed to a number of factors. The presence of feces or mucous in the rectum can mechanically alter the rectal distribution of rectally administered methohexital as well as prevent the drug from contacting the rectal mucosa. In this study, three of the 20 children (15%) who received methohexital rectally defecated after receiving the drug. This is consistent with the incidence of defecation (13%) reported in a previous study.[3] Despite the probability that some methohexital was expelled during defecation, two patients in our study fell asleep just prior to defecating; the remaining patient did not fall asleep.

Although we were unable to show any relationship between the methohexital plasma concentration or the effect of the drug and the presence or absence of feces in the rectum, some anesthesiologists have suggested that emptying the lower gastrointestinal tract of feces may improve the effectiveness of rectally administered methohexital. We have not routinely administered enemas to children prior to giving methohexital rectally because we have had some children remain awake despite preoperative enemas.

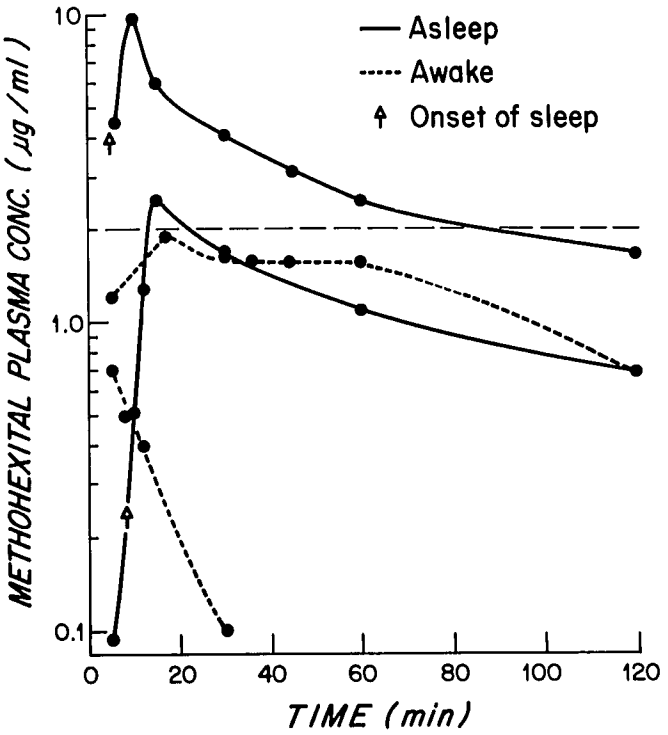

FIG. 2. Plasma methohexital concentration time curves of the patient with the highest and of the patient with the lowest plasma concentration in the group that fell asleep and in the group that remained awake.

Another factor that can alter the systemic bioavailability of rectally administered drugs is the venous distribution of the absorbed drug.[4] Methohexital is a drug that is metabolized rapidly by the liver.[5,6] If a large quantity of this drug is distributed to that portion of the hemorrhoidal plexus that drains into the portal system before reaching the systemic circulation, the brain plasma concentration will be lower than that attained if the same quantity of drug is distributed into the portion of the hemorroidal plexus that drains into the inferior vena cava.

Although rectal disease and conditions that distend rectal veins and alter hemorrhoidal plexus blood flow can affect drug absorption, it is unlikely that our results can be explained on this basis, since none of our patients had evidence of these conditions.

The location of the drug administration catheter tip at the time of methohexital deposition varied with each

patient. The study protocol did not specify the location of the catheter tip, because one of the purposes of this study was to determine methohexital plasma concentrations following the usual clinical method of administering methohexital rectally. It is possible that our results could have been more uniform had we eliminated the intersubject variability in the location of the tip of the drug administration catheter in the rectum. However, since we had no way of determining the exact length of the rectum of each child, the local distribution pattern of rectally deposited drug, the rate of rectal drug absorption, and the exact distribution of blood flow from the various areas of the rectum of each child, one can only speculate on the effect of the variation in the location of the catheter tip in our subjects.

Since the total amount of drug absorbed and the rate of absorption of rectally administered methohexital could not be determined accurately, we did not attempt to further describe the pharmacokinetics of methohexital.

In summary, the state of consciousness of a child after receiving methohexital rectally can be correlated with the concentration of methohexital in plasma. Sleep occurred in all children that had peak methohexital plasma concentrations above 2 μg/ml, while sedation varied at concentrations below this level.

The authors thank Julie Dell'Orfano for her help with the patients and their parents.

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