Dissolving Methohexital in a Lipid Emulsion Reduces Pain Associated with Intravenous Injection

Per Westrin, M.D., Ph.D.,* Christer Jonmarker, M.D., Ph.D.,† Olof Werner, M.D., Ph.D.†

Pain often accompanies intravenous injection of 1% methohexital. The aim of the present study was to test whether pain on injection could be reduced by dissolving methohexital in a lipid emulsion (study A) and whether this would affect anesthetic potency (study B). In study A, 24 healthy volunteers, 36 ± 1 yr (mean ± SE), were given 1 ml 1% methohexital in saline, 1 ml 1% methohexital in lipid emulsion, and 5 ml 0.1% methohexital in saline in random order. The injections were given in a small vein in the forearm at 5-min intervals. One minute after each injection, the subject was asked to assess the injection pain on a visual analog scale (0–100 mm). The pain score (median [range]) was 44.5 (0–77) after 1% methohexital in saline, 0.5 (0–26) after 1% methohexital in a lipid emulsion, and 1.0 (0–26) after 0.1% methohexital in saline. The pain score for 1% methohexital in saline was significantly greater than those for the other two solutions (P < 0.001 for each comparison). In study B, 42 patients, 41 ± 3 yr, were given 1% methohexital in lipid emulsion (n = 22) or 1% methohexital in saline (n = 20). A bolus of either solution was administered over 10 s, and the patient was considered asleep if there was no gross movement or response to verbal command 40–70 s after injection. Using these criteria, the methohexital dose required for satisfactory induction in 50% of patients (ED50) was 1.2 ± 0.1 mg/kg for 1% methohexital in lipid emulsion and 1.3 ± 0.1 mg/kg for 1% methohexital in saline (not significant). It is concluded that dissolving methohexital in a lipid emulsion almost abolishes pain on injection but does not reduce anesthetic potency. (Key words: Anesthetics, intravenous methohexital. Pain injection.)

Methohexital gives more rapid recovery and causes less postoperative drowsiness than thiopental. One of the disadvantages of methohexital, however, is the pain associated with its injection into small-diameter veins. This is usually well tolerated by adults but may be a problem in pediatric anesthesia.

It has previously been reported that the injection pain associated with intravenous diazepam is reduced when the drug is given in lipid emulsion. The aim of the present study was to test whether the injection pain caused by methohexital could be reduced in a similar manner (study A) and whether this would affect anesthetic potency (study B).

Materials and Methods

STUDY A

After institutional approval, informed consent was obtained from 24 healthy volunteers (anesthesiologists) 36 ± 1 yr of age (mean ± standard error [SE]) and ASA physical status I. A 24-G catheter was inserted through an intradermal wheal of 0.05 ml of 1% lidocaine into a small vein on the palmar aspect of the forearm. The subjects were familiarized with a 100-mm visual analog scale (VAS) with endpoints “no pain” and “very painful” and were instructed to spontaneously report pain or discomfort in the arm during the test period. Between the VAS assessments the subjects rested comfortably on a couch with their eyes covered.

Three different solutions were tested: 1 ml 1% methohexital in saline; 1 ml 1% methohexital in a lipid emulsion (Intralipid® Kabi Pharmacia Pharmaceuticals); and 5 ml 0.1% methohexital in saline. To keep the investigator blinded, three “control syringes” containing 1 ml saline, 1 ml lipid emulsion (Intralipid®), and 5 ml saline were also included. The response to six different solutions was thus recorded in random order, using a Latin square design.

The injectates were at room temperature (23°C), and were given over 10 s through a three-way stopcock attached to a thin catheter. The deadspace of the tubing was 0.5 ml, and the injectate was therefore flushed in with 0.5 ml isotonic saline. Care was taken to keep the subjects unaware of the exact moment when the injection was given. One min after administration of the test solution, the subject was asked to assess the pain on the VAS. The intravenous catheter was flushed with 5 ml saline and the subject was then allowed to rest 5 min before the next test solution was given. All solutions were prepared within 2 h before the study and were kept in coded syringes (see Appendix). Using Wilcoxon’s matched-pairs signed-ranks test, two comparisons were made: 1% methohexital in saline versus 1% methohexital in lipid emulsion and 1% methohexital in saline versus 0.1% methohexital in saline. P < 0.05 was considered to indicate statistical significance.

STUDY B

Forty-two patients, ASA physical status I, scheduled for arthroscopy of the knee, hernia repair, or operation

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for varicose veins participated. The study was approved by the local Human Studies Committee, and informed consent was obtained from each patient. The patients fasted for at least 6 h preoperatively. Patients with allergies were excluded from the study. No preanesthetic medication was given.

The dose required for satisfactory induction in 50% of patients (ED₉₀) was obtained by the "up and down method." The patients were randomly assigned to induction with either 1% methohexital in lipid emulsion or 1% methohexital in saline. The randomization was stratified by sex and age (greater or less than 40 yr). The resulting male/female ratios, age, and weight were 11/11, 41 ± 5 yr, and 72 ± 3 kg in the methohexital/lipid emulsion group and 9/11, 41 ± 4, and 70 ± 3, respectively, in the methohexital/saline group. The first patient in each group was given 1.0 mg/kg methohexital over 10 s in a large arm vein followed by 5 ml saline. Forty seconds after injection, the chin was gently moved into the sniffing position; the anesthesia mask was placed over the face; and the response to verbal command was recorded. Care was taken to avoid painful stimulation while lifting the chin and while holding the anesthesia mask.

The response during the following 30 s of O₂ breathing was judged by an observer unaware of the administered solution and dose. Blinding was achieved by covering the injection site with a towel during induction. If the patient coughed, moved the head or trunk, lifted an elbow or a foot from the table, or opened eyes on command, induction was classified as unsatisfactory and additional methohexital was given as needed. The dose chosen for the next patient in that group was then increased. If the patient did not move or showed only minor movements of a hand or foot, and did not open eyes on command, induction was classified as satisfactory. A smaller methohexital dose was then selected for the subsequent patient. The doses were spaced evenly on a logarithmic scale (Fig. 2). After the 70-s study period, general anesthesia was established with halothane or isoflurane in N₂O and O₂.

Systolic blood pressure and heart rate were measured just before and 70 s after the methohexital bolus. The incidence of pain on injection, apnea lasting longer than 30 s, and excitatory phenomena such as hiccups or muscle twitches in the face, arms, or legs, were recorded.

ED₉₀ was calculated as described by Dixon. The method allows estimation of ED₉₀ from a relatively small sample size and has been used to determine halothane and isoflurane MAC. To determine the SE of the estimated ED₉₀ in each group, ED₉₀ was determined in subgroups of consecutively studied patients, each with a "nominal sample size" of two. (The nominal sample size is the number of patients, beginning with the first pair of patients with unlike responses. A series of, for example, unsatisfactory–unsatisfactory–satisfactory has a nominal sample size of two). Differences between the two study groups and changes in heart rate and blood pressure within groups were analyzed with the two-sided t test for unpaired and paired data, respectively. P < 0.05 was considered to indicate statistical significance.

**Results**

**STUDY A**

The incidence of spontaneously reported pain or discomfort and the pain scores are shown in figure 1. The pain score (median [range]) was 44.5 (0–77) after 1% methohexital in saline, which was significantly greater than

<table>
<thead>
<tr>
<th>Solution</th>
<th>Spontaneous report of Pain</th>
<th>VAS score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>saline 1 ml</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>saline 5 ml</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Intralipid 1 ml</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>1% met/sal 1 ml</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>1% met/lip 1 ml</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>0.1% met/sal 5 ml</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**Fig. 1.** Response to injection of six different solutions in a small arm vein in 24 volunteers (study A). The pain response indicated on a 100-mm visual analog scale is given as mean ± SE. met = methohexital; sal = saline; lip = lipid emulsion.
Methohexital in saline
Not asleep
Asleep

Methohexital in lipid emulsion
Not asleep
Asleep

$E_D^{50}$ dose, mg/kg

10 $^{-0.08}$ 10 $^0$ 10 $^{0.08}$ 10 $^{0.16}$ 10 $^{0.24}$
0.8 1.0 1.2 1.4 1.7

**Fig. 2.** Comparison of $E_D^{50}$ for induction of anesthesia with 1% methohexital/saline and 1% methohexital/lipid emulsion (study B). Each filled circle represents one patient. The position of the circle along the horizontal line indicates the administered dose. The position of the circle below or above the line indicates whether the patient had a satisfactory induction or not. The dose expressed as an exponential and the corresponding decimal value are shown.

the 0.5 (0–26) observed after 1% methohexital in lipid emulsion, and the 1.0 (0–26) noted after 0.1% methohexital in saline ($P < 0.001$ for each comparison). Transient drowsiness resolving within a few minutes was recorded after administration of 52 of the 72 injectates containing methohexital.

**STUDY B**

$E_D^{50}$ (mean ± SE) was 1.2 ± 0.1 mg/kg for methohexital in lipid emulsion and 1.1 ± 0.1 mg/kg for methohexital in saline (not significant). Individual responses in each group are shown in figure 2. Heart rate increased significantly during induction in both groups, but there were no significant differences in heart rate or systolic blood pressure between the two groups (table 1). No patient developed bradycardia (heart rate less than 50 beats/min) or hypotension (systolic blood pressure less than 80% of preinduction value). Apnea lasting longer than 30 s occurred in two patients in the methohexital/saline group and in one in the methohexital/lipid emulsion group. One patient in the methohexital/saline group, who was given methohexital through a catheter placed on the dorsum of the hand, spontaneously reported pain on injection. Muscle twitches or hiccups occurred in six patients in the methohexital/lipid emulsion group and in five patients in the methohexital/saline group.

**Discussion**

In one of the first clinical reports on the use of 1% methohexital in aqueous solution for intravenous induction, Taylor and Stoelting reported a 60% incidence of pain at the site of injection and concluded that this and muscular twitching were the two chief disadvantages. Methohexital does not seem to be associated with a high risk for tissue damage if accidentally injected perivascularly, but the occurrence of pain on injection has been confirmed by subsequent studies.

We found that pain associated with methohexital injection was almost abolished when the drug was mixed with a lipid emulsion. The VAS score indicated that the effect was similar to that obtained when diluting the drug in saline to an 0.1% solution (fig. 1). In the present study, a Latin square design, in which the different solutions were assessed in random order, was used. In this way we tried to avoid systematic errors, e.g., those caused by the slight drowsiness or possible antanalgesic effects following methohexital injection, which could have affected the response to the subsequent injection.

Although pain on injection of drugs is common, its causes are largely unknown. Drugs with osmolality or $pH$ extremely different from that of blood can be expected to cause pain when injected into small veins, but why 1% methohexital is more prone to cause pain than 2.5% thiopental, which has similar osmolality and $pH$, is not

**Table 1. Heart Rate and Blood Pressure during Induction of Anesthesia in 42 Patients (Study B)**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>n</th>
<th>Methohexital Dose (mg/kg)</th>
<th>Systolic Blood Pressure (mmHg)</th>
<th>Heart Rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before Induction</td>
<td>70 s after Induction</td>
</tr>
<tr>
<td>Methohexital in saline</td>
<td>20</td>
<td>1.4 ± 0.1</td>
<td>192 ± 5</td>
<td>122 ± 4</td>
</tr>
<tr>
<td>Methohexital in lipid emulsion</td>
<td>22</td>
<td>1.5 ± 0.1</td>
<td>126 ± 4</td>
<td>123 ± 4</td>
</tr>
</tbody>
</table>

Mean ± SE. The methohexital dose includes supplementary doses given to patients who did not fall asleep after the initial doses.
METHOHEXITAL DISSOLVED IN A LIPID EMULSION

The use of a lipid emulsion has previously been shown to be effective in decreasing pain associated with diazepam injection. Some of the beneficial effects observed with the diazepam emulsion may have been related to avoidance of the solvent propylene glycol, but other studies suggest that lipid emulsion may, in fact, actively decrease the incidence of pain and vascular complications. Simpson et al. found that methohexital mixed with or preceded by lidocaine decreased injection pain. This was not tested in the present study, but their results—the incidence of injection pain was approximately halved—and our clinical experience with lidocaine injection indicate that this method would be less efficient than the use of a lipid emulsion. A third method to decrease pain is to dilute the drug. We did not assess different dilutions of methohexital, but preliminary tests showed that 0.2% methohexital still caused pain during injection; we therefore decided to study the effect of 0.1% methohexital. Although the VAS scores were similar for this dilution and for methohexital in lipid emulsion, the former necessitates great volumes and large syringes. It is possible, however, that a combination of the two latter methods, e.g., 0.5% methohexital mixed with lidocaine, would be efficient and clinically practical.

There was no significant difference in ED50 between methohexital/saline and methohexital/lipid emulsion (fig. 2). Absence of the lid reflex was not used as an indicator of anesthesia. A previous study and preliminary trials indicated that the reflex would be difficult to evaluate because methohexital sometimes causes muscle twitches in the face. We therefore chose to use acceptance of the face mask and response to verbal command when assessing induction. When these criteria were used, the dose requirement for satisfactory induction in 50% of patients was 1.1–1.2 mg/kg (fig. 2), which is in agreement with findings by other authors. Clarke et al. gave a methohexital bolus into an antecubital vein and found that 90% of patients stopped counting within 11 s after 1.2 mg/kg. Also, the induction dose suggested by Fagerén and Avram is 1.5 mg/kg, which is close to the mean total dose given in our patients (table 1). In the present study, the increase in heart rate and the incidences of excitatory phenomena and apnea were similar with the two preparations and agree with earlier studies. In study B, the cannula was inserted into a large vein, which explains the lower incidence of spontaneously reported pain on injection than in study A.

Although we found no difference in ED50 between the lipid emulsion and saline groups in the present study, others have found that the solvent may affect bioavailability. Fee et al. found that the plasma concentration after intravenous injection of diazepam was less when the drug was dissolved in lipid emulsion than when dissolved in propylene glycol, and it has been reported that a greater diazepam dose is needed when using the emulsified formulation. The induction dose of propofol also needs to be increased when the drug is dissolved in a lipid emulsion. Cummings et al. noted that the induction dose of propofol in lipid emulsion was 2.5 mg/kg, and Kay et al. reported an induction dose of 2.0 mg/kg with a Cremofor EL preparation. Thus, dissolving drugs in lipid emulsion seem to decrease the bioavailability of some drugs. In vitro, the lipid droplets in the mixture are so small (about 0.2 μm in diameter) that one would expect very rapid diffusion of the drug from oil to blood. Fee et al. have suggested that the fat particles may coalesce after injection into the blood, interfering with the diffusion of the drug out of the lipid phase. Sodium methohexital is more water-soluble than diazepam and propofol, and therefore a smaller fraction of the drug will be dissolved in the lipid phase. This may explain why similar induction doses were observed with the two preparations in the present study.

In conclusion, we found that dissolving methohexital in a lipid emulsion almost abolished pain on injection but did not affect the potency or other characteristics of methohexital induction. The mixture may be useful during short procedures when rapid recovery is desired and when only small veins are accessible, e.g., in pain-prone patients scheduled for cardioversion or electroconvulsive therapy. The methohexital/lipid emulsion also may be useful in young children scheduled for ambulatory procedures.

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References


Appendix

The 1% methohexitone/lipid emulsion solution was prepared by first adding 1 or 5 ml saline to a 100- or 500-mg vial of methohexitone sodium (Brietal®, Lilly). When the solution was clear on visual inspection, either 9 or 45 ml of 20% lipid emulsion (Intralipid® Kabi Pharmacia Pharmaceuticals, Sweden) was added to produce a 10-ml/ml solution, and the vial was shaken and inspected. To test whether the mixture was stable, it and a reference sample containing saline and Intralipid® were left at room temperature for at least 2 h and again inspected for signs of precipitation, flocculation, or coalescence. The samples also were microscopically examined, and the size of the droplets were measured. Neither test indicated precipitation of methohexitone or any change in the stability of the Intralipid® emulsion. The size of the droplets (about 0.2 μm) was the same in the two samples.