The Hemodynamic Consequences of High-dose Methohexitol Anesthesia in Humans

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The hemodynamic, electroencephalographic (EEG), and metabolic effects of a high-dose methohexitol anesthetic were examined in eight neurosurgical patients. The patients were studied at rest and at 15-min intervals during a 60-min infusion of the drug, given at a rate of 0.40 mg·kg⁻¹·min⁻¹ (total dose 24 mg/kg). Ventilation was controlled with oxygen/air (FIO₂ = 0.50), and fluid was infused at a rate sufficient to maintain pulmonary capillary wedge (PCW) pressures at control values (8 ± 2 mmHg, mean ± SD). Serum methohexitol concentrations increased progressively, reaching values of 11.7 ± 2.9 µg/ml at t = 30 min and 18.1 ± 10.8 µg/ml at t = 60 min. Characteristic barbiturate-induced EEG changes were noted, with isoelectricity achieved at t = 28 ± 13 min.

Methohexitol infusion resulted in significant reductions in arterial pressure (84% of control at t = 60 min), systemic vascular resistances (83% of control at t = 60 min), right and left ventricular stroke work indices (65% and 68% of control, respectively at t = 60 min), and total body O₂ consumption (76% of control at t = 60 min). In addition, a progressive dose-related decrease in stroke volume index was noted (50.1 ± 8.0 ml·beat⁻¹·m⁻² at t = 0, 48.1 ± 10.5 ml·beat⁻¹·m⁻² at t = 60 [80% of control]). This occurred in spite of unchanged ventricular filling pressures. However, cardiac index was well maintained (unchanged at t = 60 min) because of increases in heart rate (123% of control at t = 60 min). There was no change in PaO₂, PaCO₂, or pulmonary vascular resistance.

These data demonstrate that doses of methohexitol sufficient to produce profound EEG suppression are accompanied by both vasodilation and some depression of myocardial function, even when ventricular filling pressures are maintained. Nevertheless, the magnitude of these changes suggests that high doses of methohexitol may be a hemodynamically acceptable form of anesthesia for certain restricted neurosurgical procedures. However, refractory postoperative seizures occurring in three patients indicate that this anesthetic technique has potentially serious associated difficulties. For this latter reason, the authors have suspended their use of methohexitol and are examining the utility of alternative barbiturates. (Key words: Anesthesia: neurosurgical, Anesthetics, intravenous: methohexitol. Brain: arteriovenous malformation; convulsions; electroencephalogram. Complications: convulsions. Heart: myocardial function.)

LARGE DOSES OF BARBITURATES have been advocated for the management of several neurosurgical problems. These include the following: 1) the reduction of brain bulk to facilitate surgical access; 2) the control of intracranial hypertension; 3) protection of the brain during induced ischemia, such as that produced by hypotension or vessel occlusion; 4) the treatment of focal ischemic insults, i.e., stroke; and 5) the control of seizure activity, particularly status epilepticus. However, in spite of experimental support for such uses, barbiturates seldom are employed so clinically. One major reason involves concerns over the cardiovascular effects of the requisite large drug doses.

The hemodynamic changes produced by the anesthetic barbiturates have been the subject of many investigations. Unfortunately, most studies have only limited relevance to the foregoing applications because of the small doses employed, and few investigators have been able to examine the consequences of much larger drug doses. However, since early 1980, we have been involved in the care of 23 patients undergoing staged removal of large and/or deeply seated arteriovenous malformations (AVM), one patient with a large, highly vascular meningioma and another with a critically situated intracranial aneurysm (total 43 procedures). In 18 of these cases (all cases after 11/81), a single-agent barbiturate anesthetic was selected, and in 11 the chosen drug was methohexitol. The current report discusses the hemodynamic, metabolic, and electroencephalographic effects of a high-dose (24 mg/kg) methohexitol induction performed in eight of these individulals.

Materials and Methods

Eight neurosurgical patients ranging in age from 12 to 58 years were studied. A ninth patient received methohexitol, but technical failures prevented complete data collection. Two other earlier patients received different doses of the drug. Except for their neurosurgical disorders, they were free of other disease. All were taking either prophylactic or therapeutic anticonvulsants, and all were alert and intellectually intact. In each case, a high-dose barbiturate anesthetic was selected and was administered with the full and detailed informed consent of the patients (or parents). Separate informed consent was obtained for the specific hemodynamic measurements and blood samples used in these investigations.
Studies were approved by the Human Experimentation Committee of the University of California, San Diego School of Medicine.

Premedication consisted of lorazepam 2–4 mg, po, the night before surgery and diazepam 5–10 mg, po in the early morning. Morphine 2–5 mg was given iv in the operating room. The patients were sleepy but responsive to conversation and command. They were placed on the operating table with the head and torso approximately 5 degrees above the horizontal (table flexed, legs flat). Monitored vascular variables consisted of heart rate (HR); arterial pressure (BP); right atrial (RAP), pulmonary arterial (PAP), and pulmonary capillary wedge pressures (PCWP); and thermodilution cardiac output (CO) (measured in triplicate, using an Edwards 9520A® computer and a 7 or 7.5 F, thermistor-tipped Swan-Ganz® catheter).§ All pressures were referenced to the level of the right atrium, were recorded at end expiration, and are expressed as electrical means. The electrocardiogram (ECG) also was monitored in each patient along with a two-channel electroencephalogram (bipolar leads FP1-O1, FP2-O2, Beckman Accu trace®). Expired CO₂ (sampled at the mouth) was measured using an infrared analyzer (Beckman LB-II®) or a mass spectrometer (Chemetron®), while inspired oxygen concentration (Fİ₀₂) was monitored using a polarographic instrument. Temperature was recorded in the pulmonary artery, using the PA-catheter thermister and cardiac output computer.

After the monitoring devices were in place the patients were left undisturbed on the operating table for approximately 10 min. An anesthesia mask then was placed on the face, and 50% oxygen (in air) was administered for an additional 10 min. Control data were obtained, and an infusion of methohexital (5 g in 250 ml of 5% dextrose in water) was started at a rate of 0.40 mg·kg⁻¹·min⁻¹, using an IVAC 630® pump.¶ This rate was not changed for the next 60 min (total dose over 1 h = 24 mg/kg). Two to five minutes after the start of drug infusion, a combination of pancuronium and metocurine (0.03 mg/kg pancuronium + 0.12 mg/kg metocurine14 was administered and manual ventilation begun by mask. A nasopharyngeal airway was placed when necessary. FlO₂ was kept at 0.50 (still in air), while end-tidal expired CO₂ was maintained between 4.0 and 4.5%. Care was taken to keep end-expiratory airway pressure at zero, and temperature was held at 36–37°C using warming blankets and a heated humidifier. The electroencephalogram (EEG) was recorded continuously.

The methohexital infusion was continued for 60 min. During this period, hemodynamic variables were recorded at 15-min intervals. Throughout the experimental period (0–60 min after the start of methohexital infusion), lactated Ringer’s solution was infused at a rate sufficient to maintain PCWP at control values (see “Discussion”). Immediately after recording data at t = 45 min (i.e., 12–13 min before the t = 60 min data point) a nasotracheal tube was placed. Except for this and the placement of the nasopharyngeal airway, no other stimulus was permitted during the 60-min induction period. After data collection at t = 60 min, the methohexital infusion rate was reduced and surgical preparation proceeded. Drug administration thereafter was titrated to maintain EEG isoelectricity (infusion rates = 0.1–0.3 mg·kg⁻¹·min⁻¹). However, because of widely differing surgical requirements (patient position, the use of hypothermia and/or induced hypotension), systematic data collection was not carried out beyond the induction period.

Arterial samples for the determination of serum methohexital concentrations were drawn at 0, 5, 10, 15, 20, 25, 30, 45, and 60 min after the start of drug infusion. Drug concentrations were measured using high-performance liquid chromatography15 and expressed as µg/ml. In addition, paired arterial and mixed venous blood samples were obtained at 0, 15, 30, 45, and 60 min for the determination of P O₂, P CO₂, pH, hematocrit (Hct%), hemoglobin concentration (Hgb-g/dl), per cent Hgb saturation, and O₂ content (using an Instrumentation Laboratories CO-oximeter). Calculated variables (obtained using standard formulas) were expressed as indices (per m²) and include cardiac index (CI) (l·min⁻¹·m⁻²), stroke volume index (SVI) (ml·beat⁻¹·m⁻²), systemic and pulmonary vascular resistance indices (SVRI and PVRI) (mmHg·l·min⁻¹·m⁻²) and both left and right ventricular stroke work indices (LVSWI and RVSWI) (mmHg·ml·beat⁻¹·m⁻²). Oxygen consumption (expressed as ml·min⁻¹·m⁻²) was calculated by the Fick equation.

Statistical analysis was performed using an analysis of variance for repeated measures and paired t tests with Bonferroni corrections.

Results

All patients had comparable preinduction EEGs, characterized by high frequency, low-amplitude activity with
occasional alpha patterns and intermittent spindling. Methohexital infusions produced the characteristic sequence of changes noted for other barbiturates.\textsuperscript{16-18} High-amplitude, rhythmic activity appeared at 2.0 ± 0.5 min (mean ± SD), and initial, brief periods of suppression were noted at 8.0 ± 3.2 min. “Deep” burst-suppression patterns (8–12 bursts/min) were evident at 18.4 ± 9.0 min and the EEG was isoelectric at 28 ± 13 min. The changes in serum methohexital concentrations (with EEG landmarks noted) are shown in figure 1. The curve is characterized by a rapid increase in the first 5 min (from 0 to 7.1 ± 1.0 μg/ml) and a more gradual increase over the remainder of the study, reaching a value of 18.1 ± 10.8 μg/ml at 60 min.

Hemodynamic changes are summarized in table 1 and in figure 2A–D. Since fluids were administered to keep PCWP at control values, no changes in PCWP were expected and none were noted. In addition, no changes were seen in either RAP or PAP. CI increased significantly at \( t = 15 \) min and then returned toward control levels such that CI at \( t = 60 \) min was unchanged from control (fig. 2A). The maintenance of CI resulted from an increase in HR (fig. 2B), which acted to compensate for a progressive decrease in SVI, from 50.1 ± 9 ml·beat\(^{-1}\)·m\(^{-2}\) in the control state to 40.1 ± 10.2 ml·beat\(^{-1}\)·m\(^{-2}\) at 60 min (fig. 2C). BP decreased as a result of a reduction in SVRI from 21.1 ± 5 mmHg·l\(^{-1}\)·min·m\(^{-2}\) at \( t = 0 \) to 15.2 ± 3.8 mmHg·l\(^{-1}\)·min·m\(^{-2}\) at \( t = 15 \) min and 17.5 ± 33.8 mmHg·l\(^{-1}\)·min·m\(^{-2}\) at \( t = 60 \) min (fig. 2D). There were no changes in PVR. Both LV and RVSWI decreased progressively, reaching values of 65 and 68% of control, respectively, at \( t = 60 \) min (table 1).

There were no changes in \( \text{PaO}_2 \), despite the onset of paralysis and manual ventilation. Neither \( \text{Paco}_2 \) nor \( \text{pH} \) changed during the first 45 min of the study period. The decrease in \( \text{Paco}_2 \) (and the increase in \( \text{pH} \)) seen at \( t = 60 \) min occurred after endotracheal intubation. Calculated \( \text{O}_2 \) consumption fell progressively, from 91 ml·min\(^{-1}\)·m\(^{-2}\) at \( t = 0 \) to 69 ml·min\(^{-1}\)·m\(^{-2}\) at \( t = 60 \). The change in Hgb concentration reflects the dilutional effects of the volume infusion used to maintain PCWP during the study.

Of the patients reported herein, there was one death, due to sepsis and disseminated intravascular coagulation occurring on the fifth postoperative day. The remaining patients recovered with no new neurologic deficits and there were no untoward intraoperative events. However, three of the patients developed clinical and electroencephalographic seizures in the early (6–12 h) postoperative period. In each case, these seizures were surprisingly refractory to therapy, although all resolved within several hours. No seizure activity was noted among other barbiturate- (e.g., thiopental) treated patients, and postoperative seizures were not seen among patients who did not receive barbiturate anesthetics.

There were no evident problems of cerebral edema that could be attributed to the crystalloid infusions employed in this study.

**Discussion**

Numerous problems are encountered when one attempts to interpret the results of previous experiments that have examined the hemodynamic effects of the anesthetic barbiturates in humans. For example, most workers have studied the changes that follow either the rapid infusion or bolus administration of the selected drug. While this approach has some clinical relevance, the rapidly changing drug concentrations introduce a host of difficulties including uncertain blood-tissue equilibration and the problem of determining an appropriate...
Table 1. Hemodynamic, Respiratory, and Metabolic Data Obtained During the 60-minute, High-dose Infusion Period

| time for data collection (particularly since the measurements themselves may take several minutes). This situation may be further complicated by the concomitant administration of other anesthetics (e.g., N₂O), by the failure to control PaCO₂ or by surgical stimulation. In addition, direct “myocardial” effects of the drug are difficult to delineate in the face of simultaneous changes in venous return (and ventricular filling pressures), contractility, heart rate, and “afterload.” Finally, with respect to the neurosurgical use of these drugs, few human studies have examined the hemodynamic effects of the large barbiturate doses needed to produce maximal cerebral metabolic suppression (i.e., which yield an isoelectric EEG).¹⁹

The current protocol has allowed us to evaluate the changes produced by large doses of methohexitol in a manner that minimized at least some of the aforementioned problems. The study was performed in patients without cardiovascular disease and with normal, preinduction hemodynamic profiles. Methohexitol was infused at a fixed rate to produce progressively increasing blood concentrations. Since drug levels during infusion changed slowly (compared with a bolus injection), there was time for blood-tissue equilibration. In addition, cardiovascular function (and blood levels) was relatively “stable” during the 1–3 min periods needed for data collection. Control data were obtained in a “resting” state, PaCO₂ was controlled, and central nervous system (CNS) activity was monitored (by EEG) to permit some correlation between anesthetic “depth,” serum methohexitol concentrations, and hemodynamic function. Surgical stimulation was absent, and, while there were some changes in BP and HR produced by tracheal intubation, these were transient and no data were collected until 12–13 min later. Finally, an attempt was made to control left ventricular filling pressures by infusing fluids to maintain PCWP. The goal was to maintain a constant ventricular “preload” (at least within the limits associated with trying to equate PCWP with preload) and thus improve our ability to interpret the cause of any observed changes in cardiovascular function.

Certain portions of our results must be examined more closely. Large volumes of fluid (1–2 l) were needed to maintain the desired stable filling pressures. This suggests that methohexitol caused a substantial degree of venodilation, the magnitude of which is indicated by the dilutional decrease in Hgb concentration (from 13.0 to 11.3 g/dl at t = 60 min).** Similar evidence of venodilation has been noted with thiopental. Eckstein et al. reported a decrease in venous tone,²⁰ while both Etsen and Li²¹ and Flickinger et al.²² measured a decrease in “intrathoracic blood volume.” Reductions in RAP (and/or PCWP) with thiopental²³–²⁵ likewise have been reported. Dobkin noted a similar decrease in RAP after methohexitol,²³ but few other complete studies of methohexitol in humans are available. Contrary to our data,
both Prys-Roberts et al.\textsuperscript{26} and Allen et al.\textsuperscript{27} reported significant increases in RAP following modest doses of methohexital. However, in both of these studies, the patients breathed spontaneously and \textit{Paco}_2 increased. The individuals studied by Prys-Roberts et al.\textit{ also were given nitrous oxide.\textsuperscript{26} Methohexital induced increases in central venous pressure have been noted in dogs,\textsuperscript{28} but these animals already had been anesthetized with pentobarbital and had been subjected to extensive surgical preparation.}

Additional evidence of vasodilation is seen in the observed reductions in SVRI. Similar reductions in systemic vascular resistance (SVR) after methohexital and thiopental have been described,\textsuperscript{23,25-27} while several groups have recorded increases in SVR following thiopental injection.\textsuperscript{17,22,27} However, in all of these latter experiments CI decreased, suggesting that the increase in SVR may have been the result of reflex vasoconstriction. Our data support the view that reflex control of systemic resistance persists, since the lowest SVRI values occurred at \(t = 15\) min, with a gradual increase noted at \(t = 30, 45,\) and 60 min, in spite of increasing blood methohexital concentrations. This paralleled a gradual decrease in CI (3.8 l\cdot min\(^{-1}\)\cdot m\(^{-2}\) at \(t = 60\) min, compared with 4.5 l\cdot min\(^{-1}\)\cdot m\(^{-2}\) at \(t = 15\) min). Such a gradual compensatory change in SVRI also may explain some of the differences observed between this study and others employing bolus injections where the time for compensation is less.

Methohexital led to a progressive and dose-related decrease in SVI, from 50.1 ml\cdot beat\(^{-1}\)\cdot m\(^{-2}\) in the control state to 40.1 ml\cdot beat\(^{-1}\)\cdot m\(^{-2}\) at \(t = 60\) min. Similar changes in stroke volume have been described frequently during the administration of other barbiturates.\textsuperscript{17,21-23,25-27} Because this occurred in spite of well-maintained right and left ventricular filling pressures (and a reduced SVR), it must be taken as evidence of depressed myocardial performance. Only the increase in HR prevented a decrease in CI. It is not clear, however, whether these changes in HR were strictly "compensatory," \textit{i.e.}, a reflection of an intact reflex arc, since they resulted in an increase in CI at \(t = 15\) min.
It is possible that the increase in HR was a direct effect of the drug, perhaps acting by an inhibition of vagal innervation of the heart. Such an effect has been recorded in animals.29

Several clinical comments are in order. Barbiturate anesthesia was selected for this unique group of individuals for several reasons. Patients harboring large AVMs are at particular risk for two intraoperative events: 1) ischemic brain injury, caused by vessel occlusion and/or retractor pressure, which also may be compounded by the need for induced hypotension, and 2) severe "malignant" brain swelling, also known as the reperfusion breakthrough syndrome.30 The protective and therapeutic effects of the barbiturates in cerebral ischemia are well supported experimentally.4-9 Furthermore, the potentially lethal reperfusion syndrome has been controlled successfully in several situations by the rapid induction of high-dose barbiturate anesthesia.51,52 As a result of such considerations, we elected, beginning in late 1981, to employ barbiturates as our primary anesthetic for surgery on such high-flow lesions and have extended the indications for such an anesthetic to several other high-risk procedures. Our choice of methohexital, after an initial experience with thiopental,13 was based on its pharmacokinetic profile and our desire to avoid prolonged (days) postoperative sedation after these extremely long procedures (12–18 h). However, the occurrence of postoperative seizures in three of our patients has been disturbing. While seizures are common among patients with AVMs, we had not encountered such difficulties prior to the use of methohexital. It is of particular note that one of the three patients had no history of prior seizures. Furthermore, while postoperative 16-channel EEG recordings demonstrated a cortical focus in this patient, the entire operation had been infratentorial (pontine AVM). Methohexital is a chemical convulsant33,34 and it is possible that this was the cause of the observed events. However, no seizures (clinical or by EEG) were noted during the period of drug administration. This finding, as well as their refractory nature, suggest that a possible alternative explanation may be acute barbiturate withdrawal. Each patient had received the drug for 12–24 h.†† The infusion then was discontinued abruptly. It is probable that some tolerance developed during the infusion.35 A rapid decline in blood levels then may have led to an acute withdrawal state with concomitant seizures36 or to unmasking of a seizure focus.35 This possibility remains speculative; however, in view of the problem, we have discontinued the use of prolonged high dose methohexital anesthesia.

In summary, our results indicate that serum concentrations of methohexital even in excess of that sufficient to render the EEG isoelectric (approximately 12 μg/ml at t = 30 min—see figure 1) are associated with modest reductions in stroke volume, arterial pressure, systemic vascular resistance, and total body O2 consumption, while cardiac index was well maintained by an increase in heart rate. In addition, drug infusion appeared to result in significant "venodilation," although the cardiovascular impact of this change was minimized by the experimental design (i.e., fluid administration to maintain constant PCWP). These results suggest that methohexital in doses sufficient to achieve maximal cerebral metabolic suppression can be given with minimal cardiovascular risk, at least in healthy individuals and if ventricular filling pressures are maintained. Unfortunately, postanesthetic seizures in three of our patients suggest that methohexital may be an inappropriate agent for such use, in spite of its favorable hemodynamic and pharmacokinetic properties. Whether a "safer" anesthetic can be achieved with another—albeit longer-acting—barbiturate (thiopental, pentobarbital) or perhaps with a different class of drug (e.g., etomidate, Althesin89, etc.) remains to be demonstrated. Studies are underway to complete the examination of a similar high-dose thiopental anesthetic, and no postoperative seizure activity has yet been noted. If confirmed, these observations, combined with those noted herein, suggest that high-dose barbiturate anesthesia may have a useful, although highly limited, place in neuroanesthetic practice.

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References


†† Three of the 11 patients (including one of the seizure patients) continued to receive methohexital for up to 6 h postoperatively, during rewarming after cases in which induced hypothermia was used.
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