

# METHOHEXITAL SODIUM—A NEW ULTRASHORT ACTING BARBITURATE

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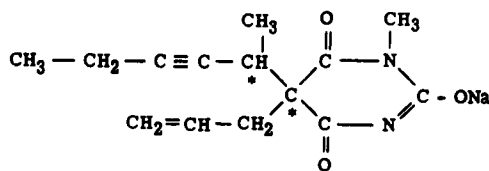
IN an attempt to find an ultrashort acting barbiturate, with greater potency and a shorter duration of action than thiopental or thiamylal, over two thousand barbiturates have been synthesized. Methohexital (Brevital) sodium is one of these barbiturates. The drug has been administered to 3,340 patients to provide anesthesia for surgery. A preliminary study of this drug warranted further clinical investigation,<sup>1</sup> the results of which form the basis of this report.

## CHEMISTRY AND PHARMACOLOGY

The chemical name of this compound is  $\alpha$  d,l 1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbituric acid sodium (fig. 1). The thiobarbiturates, thiopental (fig. 2), and thiamylal (fig. 3), have a sulphur attached to the 2-carbon, whereas methohexital has an oxygen attached to the 2-carbon. This drug thus resembles pentobarbital and secobarbital, the oxygen analogues of thiopental and thiamylal. Hexobarbital (Evipal, fig. 4), the first ultrashort acting barbiturate used extensively in clinical practice, is also an oxygen barbiturate, and differs chemically from methohexital by the presence of a cyclohexenyl and a methyl group attached to the 5-carbon.

Methohexital sodium is the high-melting-point isomer of compound 22451,<sup>2</sup> which has the same basic chemical formula, but is a mixture of the  $\alpha$  and  $\beta$  stereoisomers of d,l 1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbituric acid sodium.<sup>3</sup> The clinical trial of compound 22451 was abandoned, when generalized convulsions were reported during the use of this drug. The original material was fractionated into high- and low-melting-point isomers. With the high-melting-point isomer, methohexital, the preconvulsive electroencephalographic patterns were not seen in either cats or human beings. The short duration

of action and the lack of accumulation on repeated administration were the same for methohexital and compound 22451. The median anesthetic dose ( $AD_{50}$ ) and the lethal dose ( $LD_{50}$ ) were both determined by the intravenous injection of the drug in 30 rats. The  $AD_{50} \pm S.E.$  (standard error) was  $14.2 \pm 0.9$  mg./kg., and the  $LD_{50} \pm S.E.$  was  $31.0 \pm 2.1$  mg./kg. The average duration of action



\*Denotes centers of asymmetry

FIG. 1. Methohexital sodium (Brevital).

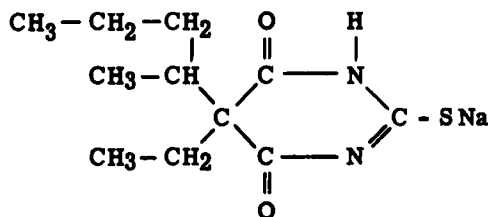


FIG. 2. Thiopental sodium (Pentothal).

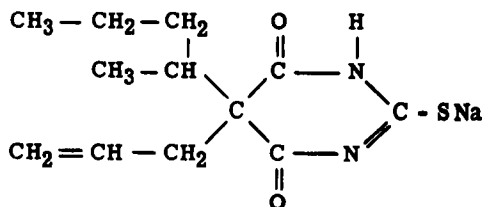


FIG. 3. Thiamylal sodium (Surital).

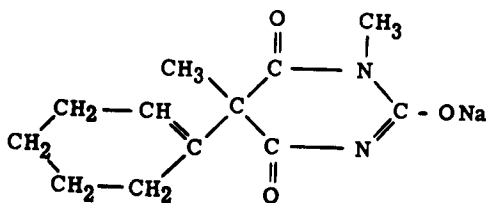


FIG. 4. Hexobarbital sodium (Evipal).

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TABLE 1  
MEDIAN ANESTHETIC DOSES AND AVERAGE DURATIONS OF ANESTHESIA IN ANIMALS<sup>1</sup>

	Methohexital Sodium			Thiopental Sodium		
	Number of Animals	AD <sub>50</sub> ± S.E. (mg., kg.)	Duration of Anesthesia (Minutes)	Number of Animals	AD <sub>50</sub> ± S.E. (mg., kg.)	Duration of Anesthesia (Minutes)
Rats	30	14.22 ± 0.94	22	30	29.0 ± 1.5	186
Mice	30	17.93 ± 0.61	18			
Dogs	15	9.74 ± 0.93	29	15	16.0 ± 0.97	142
Cats	20	5.78 ± 0.54	39	15	10.4 ± 0.92	58
Monkeys	15	4.43 ± 0.21	15	15	9.95 ± 1.39	44

was 22 minutes, and the therapeutic index with 95 per cent confidence limits was 2.2 (1.8–2.6).<sup>3</sup>

A comparison of methohexital with thiopental was made in five different species of animals. In all of the animals studied, methohexital was twice as potent (on a weight basis) as thiopental (table 1).<sup>4</sup>

The drug is stable in aqueous solution at room temperature for at least six weeks. The pH of such solutions is 11. The sodium salt is rapidly and easily soluble in distilled water and saline to produce a clear mixture.

#### CLINICAL MATERIAL

The data presented have been taken from the records of the Department of Anesthesiology at the Indiana University Medical Center. The average age of the 3,340 patients was 40 years, with a range from 3 to 89 years. The average duration of anesthesia was 109 minutes with a range of 10–540 minutes. Selection of patients was made only

with reference to the usual precautions taken with the use of any ultrashort acting barbiturate. The drug was used during all types of surgical operations (table 2).

Premedication consisted of an appropriate dose of morphine sulfate or meperidine hydrochloride, and atropine sulfate or scopolamine hydrobromide. These drugs were administered 1–1½ hours prior to the induction of anesthesia.

#### TECHNIQUE OF ADMINISTRATION

Methohexital was administered intravenously as a 1 per cent solution by intermittent injection, or as a 0.1 or 0.2 per cent solution by continuous drip infusion. The 1 per cent solution was prepared by the addition of 50 ml. of distilled water or normal saline to 500 mg. of Methohexital. The 0.1 and 0.2 per cent solutions were obtained by dissolving 500 mg. or 1000 mg. of methohexital, respectively, in 500 ml. of 5 per cent dextrose in distilled water.

The induction of anesthesia was accomplished by the administration of quantities of the drug sufficient to obtund or eliminate the lid reflex. Inhalation agents, nitrous oxide, cyclopropane, ether, or halothane were then administered by the carbon dioxide absorption closed or semiclosed and to and fro or circle technique.

Endotracheal intubation was performed, when indicated, following the intravenous injection of methohexital and succinylcholine from separate syringes. The succinylcholine was used to ensure adequate relaxation of the laryngeal and mandibular muscles.

In all operations requiring muscular relaxa-

TABLE 2  
TYPES OF SURGICAL PROCEDURES REPRESENTED  
IN THE STUDY

Intrathoracic surgery	
Cardiac	171
Pulmonary	129
General surgery	715
Peripheral vascular surgery	113
Gynecologic surgery	977
Orthopedic surgery	375
Neurosurgery	364
Eye, ear, nose and throat, genito- urinary, plastic and dental surgery	496
Total	3340

tion, metubine iodide or succinylcholine chloride were administered intravenously.

#### CLINICAL OBSERVATIONS

Anesthesia was introduced by the intravenous injection of the 1 per cent solution of methohexital. The amount of methohexital required for induction varied between 20 mg. and 250 mg. The average dose of the drug required for induction was 70 mg. The induction of anesthesia was rapid and complete in all individuals. Undesirable side effects such as hiccup, muscular twitching, apnea and circulatory depression were noted in many patients. These were closely related to the rapidity of injection and to the amount given at each injection. Patients receiving adequate hypnotic doses of methohexital injected intravenously over a 60–90 second interval seldom presented any of these untoward effects. Patients given inadequate premedication frequently developed hiccupping and mild muscular twitching.

Respiratory depression frequently followed the initial dose of methohexital. Apnea occurred in 569 patients but was transient, lasting up to three minutes. Intermittent positive pressure ventilation was required during this period. When the patient was markedly depressed by the narcotic used for premedication, or when the drug was injected rapidly, apnea occurred with great frequency. Under these circumstances apnea has been produced with as little as 40 mg. of methohexital. This initial respiratory depression subsided rapidly, permitting spontaneous respiration to be established during induction with the inhalation agents, such as cyclopropane, ether or halothane.

Sixty per cent of the patients complained of pain at the site of injection, or along the course of the vein. The intensity of the pain varied, but usually evoked a spontaneous and bitter complaint from the patient. A reassurance that the pain would subside rapidly was sufficient to calm the patient, who lost consciousness within a few seconds. Except for the few patients who required large amounts of the drug to induce unconsciousness, the patients did not recall that they had complained of pain when ques-

tioned during the postoperative period. None of these patients developed thrombophlebitis during the postoperative period.

Eighty-six patients developed marked skeletal muscle twitchings or tremors following the induction of anesthesia with methohexital. In all the degree of sedation resulting from the preanesthetic medication was inadequate. Additional amounts of methohexital controlled these muscular movements. Deepening anesthesia with other drugs such as ether, cyclopropane or halothane also stopped these movements. Clonic convulsions did not occur in any patient. No ill effects were observed as a result of the tremors in any patient, during or following anesthesia.

A fall in the blood pressure was observed in 534 patients following the administration of the initial dose of methohexital. The systolic blood pressure was depressed 10–20 mm. of mercury in 401 patients, and 30–40 mm. of mercury in 133 patients. This fall in blood pressure was transient and usually returned to the preoperative level within five minutes. No period of severe hypotension could be attributed to methohexital.

Spontaneous coughing occurred in 33 patients during the period of induction. The coughing subsided when the level of anesthesia was deepened by further injections of methohexital. This complication was not of sufficient severity to constitute a problem in the conduct of anesthesia.

During the early part of the study, a history of asthma was considered to be a contraindication to the use of methohexital. Towards the end of the study the drug was given to this group of patients. Since barbiturates containing an oxygen radical are frequently used to sedate patients during an asthmatic attack, it was believed that methohexital could be used intravenously in these patients. Forty-five patients with a history of asthma have received methohexital during anesthesia. None developed bronchospasm, nor did it occur in any of the other patients included in this study.

Respiratory depression was evident throughout the course of anesthesia. Pulmonary ventilation was usually inadequate when the level of anesthesia was adequate, and it was necessary to assist respiration. Prolonged apnea or

respiratory depression did not occur, following the termination of anesthesia.

Laryngospasm was an infrequent complication, and occurred in only 28 patients. It was usually mild and could be relieved by a further injection of methohexital, and the removal of any exciting stimulus. The insertion of oral airways in patients receiving methohexital rarely caused laryngospasm. If the patient was lightly anesthetized, he usually showed the tendency to awaken, swallow on the airway and reject it. The administration of additional methohexital allowed the patient to tolerate the presence of the airway.

Hiccups were seen in 85 patients. This complication was relieved when the level of anesthesia was deepened with methohexital or one of the other inhalation anesthetic agents. The administration of a muscle relaxant controlled the hiccupping, but as soon as the action of this drug had subsided hiccupping returned, unless anesthesia had been established with the other inhalation agents.

The maintenance of anesthesia, using methohexital in combination with nitrous oxide and oxygen, was more satisfactory when the drug was administered by continuous drip infusion. The short duration of action of methohexital necessitated frequent injections, when administered intermittently, and the continuous drip technique was found to be more convenient. A micro-drip type of filter has been found to be effective in maintaining a smooth level of sedation, and to prevent marked respiratory depression. Spontaneous respiration could be maintained easily by adjusting the drip.

The drug was an ideal preparation for rapid induction of hypnosis when inhalation anesthesia of cyclopropane, ether or halothane was anticipated. The drug was so rapidly metabolized that it did not interfere with the use of these inhalation agents.

All patients exhibited active reflexes in the operating room at the termination of surgery. Many of these patients were oriented and mentally clear. A great majority of the patients retched, with or without emesis at the termination of anesthesia while still in the operating room. This was not considered to be an unusual or serious complication following inhalation techniques and agents.

Two hundred and twenty patients vomited once or twice in the recovery room.

#### DISCUSSION

For the purpose of comparison, the records of patients who had been given thiopental and thiamylal with 75 per cent nitrous oxide and 25 per cent oxygen were selected at random from the files of this department and examined. It was believed that these three groups of patients were generally comparable. From this comparison of the mean dose for induction of anesthesia, methohexital is approximately three times as potent as thiopental, and four and one half times as potent as thiamylal. Methohexital was utilized about three times as rapidly as thiopental and one and one-half times as rapidly as thiamylal. This is in keeping with the clinical impression that recovery is more rapid following the use of methohexital.

To maintain anesthesia three times as many milligrams of thiamylal as of the other two drugs were used per hour. Since one and a half times as much thiamylal as thiopental was used for induction, the activity of thiamylal was lost approximately twice as rapidly as that of thiopental.

Gram for gram, methohexital was about four times as potent as thiamylal. Thiamylal was utilized two and one-half times as rapidly as methohexital to maintain anesthesia. In terms of anesthetic doses methohexital was utilized one and one-half as rapidly as thiamylal. This also supports the clinical impression that patients recover more promptly after the use of methohexital than after the use of thiopental and thiamylal.

Redish *et al.*<sup>5</sup> administered 1 per cent methohexital, 2.5 per cent thiopental and 5 per cent methitural to out-patients for oral surgery, at the rate of 1 ml. every 15 seconds. They found that 135 mg. of methohexital produced hypnosis equivalent to approximately 410 mg. of thiopental or 765 mg. of methitural. They concluded that the rate of recovery was significantly more rapid following the use of methohexital than from comparable doses of methitural or thiopental. Wyant, Dobkin and Aasheim,<sup>6</sup> in a comparative study of 7 intravenous anesthetic agents, found that methohexital was the most potent drug. They used

a 2.5 per cent solution of methohexital and administered the drug at the rate of 1 ml. per 1.5 seconds with a total dose of 273 mg. per square meter of body surface. This is seven and one-half times the average dose required to induce anesthesia. Awakening in these patients occurred after about twenty minutes.

Pain along the vein wherein the injection was made and muscular twitchings were the two chief disadvantages we have noted with the use of this drug. The pain following the injection of methohexital was of moderate severity, but was most disturbing because of its frequency. The rate of injection and the nature of the diluent did not affect the incidence of this complication. This is an undesirable feature which detracts from the value of using this drug to provide a pleasant induction of anesthesia. None of the patients in this series developed thrombophlebitis in the postoperative period. Methohexital was injected intravenously daily for 28 consecutive days, into 10 dogs using the same site. Gross examination of the veins used for injection revealed no change from the normal.

The muscular movements observed during the use of methohexital can be described most accurately as muscular twitchings or tremors. None of these patients developed a clonic epileptiform convulsion. Bergner<sup>7</sup> has pointed out that almost every anesthetic may be associated with some form of motor tremor or clonic spasm. Smith<sup>8</sup> has suggested that a true convulsion is cerebral in origin, whereas other movements originate at a lower level. These latter movements are not associated with the presence of toxic factors, and do not assume the serious prognosis of a cerebral convulsion. Electroencephalographic tracings obtained postoperatively from several patients, who showed gross muscular twitching during induction of anesthesia with methohexital were normal. The electroencephalographic tracings obtained during anesthesia with methohexital are similar to those obtained using thiopental anesthesia, but the change in pattern occurred more promptly, and the duration of effect electrographically was shorter.

Respiratory depression is more severe with the use of methohexital than with thiamylal or thiopental at a similar level of narcosis. The

physician who uses this drug must be familiar with the techniques of assisted or controlled ventilation, and have available the equipment to administer oxygen under positive pressure.

The observations of others<sup>5,9</sup> who have studied methohexital have been similar to those noted in this study. The drug appears a safe and satisfactory agent, and has advantages over other ultrashort acting barbiturates. Methohexital has a greater potency and a shorter duration of action. These factors allow a greater control of the level of anesthesia and a more consistent rapid awakening following the termination of anesthesia.

#### SUMMARY

Methohexital, a new ultrashort acting oxygen barbiturate, has been used safely as an intravenous anesthetic agent, by intermittent administration of a 1 per cent solution, or by the continuous administration of a 0.1 or 0.2 per cent solution in 3,340 patients.

The major disadvantages of this drug are the frequency of pain along the vein following the injection of the drug, and muscular twitchings. Respiratory depression is present when the level of anesthesia is adequate, and ventilation has to be supplemented. Laryngospasm, hiccups and coughing occurred infrequently.

Methohexital appears to have certain advantages over other ultrashort acting barbiturates in that it has a greater potency and a shorter duration of action. These factors allow better control of the level of anesthesia and a more rapid awakening following the termination of anesthesia.

Methohexital (Brevital) sodium was supplied by the Eli Lilly Research Laboratories, Indianapolis, Indiana. This work was presented at the Annual Session of the American Society of Anesthesiologists, Inc., Chicago, Illinois, November 20, 1958.

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**VOMITING OF PREGNANCY** Accepting the reflex theory of the origin of toxemias of pregnancy, it was assumed that by changing the conductivity of the nerves running from the uterus to the brain the passage of impulses from the interoceptors of the uterus could be affected and thus the desired therapeutic effect obtained. To test this assumption he treated 31 women with vomiting during pregnancy with 120 ml. procaine solution injected into the parametrium. All patients, except one, responded satisfactorily to this treatment. There were no recurrences of vomiting and the course of pregnancy was not adversely affected. (*Putilin, S. A.: Treatment of Excessive Vomiting and Salivation in Pregnancy by Parametric Nerve-Blocking with Procaine, Akush. i Ginek. 1: 100, 1958.*)

**PERPHENAZINE** A comparison of 334 patients in labor medicated with perphenazine and a control group of 122 treated with the

usual combination of meperidine, a barbiturate, and scopolamine revealed no complications with the use of perphenazine. Fetal apnea was less commonly observed in the perphenazine group than in the meperidine group. (*Cannistra, F.: Perphenazine in obstetrics, Obst. & Gynec. 14: 337 (Sept.) 1959.*)

#### **SHORTAGE OF ANESTHESIOLOGISTS**

A meeting of all chiefs of anesthesia at German universities (both West and East Germany) was held in February 1959 at Goettingen where the critical shortage of anesthesiologists in all German hospitals was discussed. It was estimated that there is a need for 2,000 specialists, whereas at present, there are only 80 certified anesthesiologists. Measures were discussed for correction of this shortage by 1975. (*Horatz, K., and Stoffregen, J.: Report on Meeting of Anesthesiologists at Goettingen on February 1, 1959, Der Anaesthetist 8: 212 (July) 1959.*)