METHITURAL SODIUM (NERAVAL® SODIUM): A NEW ULTRASHORT ACTING INTRAVENOUS ANESTHETIC

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A NEW ultrashort acting intravenous barbiturate, with minimal side effects, quick action, and rapid and complete recovery is desired in anesthesiology (1–8).

Recently, a new intravenous anesthetic, methitural sodium (Neraval® sodium), with significantly more rapid recovery and fewer side effects than thiopental sodium and thiamylal sodium was reported (9–10). This drug was introduced in Europe as "Thiogenal," and on the basis of more than 10,000 administrations there since 1954, it was reported that induction of anesthesia with methitural sodium was unaccompanied by significant changes in respiration, blood pressure or pulse rate, and recovery from ten-minute operative procedures were complete within fifteen or thirty minutes, with the patients mentally alert and ready for discharge. Vertigo, salivation, vomiting, weakness, tremors, and excitement were notably absent during anesthesia and recovery, and mild coughing was observed in only a small percentage of the cases. Incidence of laryngospasm was negligible. The drug was found well tolerated by all patients, even the aged.

Since methitural sodium appeared to be an improvement over the older drugs, a clinical investigation was attempted.

COMPARISON OF PROPERTIES

Chemical Properties.—Although thiopental sodium, thiamylal sodium and methitural sodium are chemically related, there is a marked difference in their molecular structures. Thiopental sodium has the 5-ethyl-5-(1-methylbutyl) chain on the thiobarbiturate sodium molecule. Thiamylal sodium is the same combination of an allyl radical with the 1-methylbutyl radical added to the thiobarbiturate nucleus. However, methitural sodium is structurally unique among the members of this group of anesthetic compounds in that it has a second sulfur substitution forming a special methylthioethyl radical (fig. 1). This methylthioethyl side chain is also present in methionine, one of the essential amino acids, which has been shown to have a protective action on the liver.

Physical Properties.—Thiopental sodium occurs as a yellowish white, hygroscopic powder with a disagreeable odor. Its solutions are

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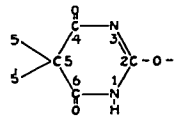
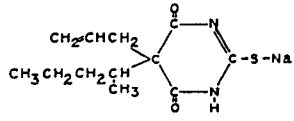
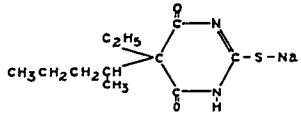
alkaline to litmus paper. It is soluble in water and in alcohol and insoluble in absolute ether, in benzene and in petroleum benzin. Its solution decomposes on standing; precipitation occurs on boiling. Thiamylal sodium is marketed as a mixture with sodium carbonate. This consists of a pale yellow, hygroscopic, agglutinated mass of crystals with no pronounced odor. It is freely soluble in water. With thiamylal sodium, as well as with thiopental sodium, the patient often complains of a disagreeable taste on induction of anesthesia. Methitural sodium is a pale yellow, very hygroscopic powder containing anhydrous sodium carbonate, and is freely soluble in water and ethyl alcohol. Its solution without sodium carbonate is clear with a pale straw color and is approximately *p*H 9.8. In solution, it is somewhat less alkaline than thiopental sodium and thiamylal sodium.



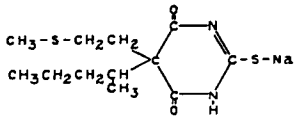
Barbiturate nucleus



Thiamylal sodium (Surital® sodium)
5-allyl-5-(1-methylbutyl)-2-thiobarbiturate sodium)



Thiopental sodium (Pentothal® sodium)
5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate sodium



Methitural sodium (Neraval® sodium)
5-(1-methylbutyl)-5-[2-(methylthio)ethyl]-2-thiobarbiturate sodium

FIG. 1. Structural relationship of thiopental sodium, thiamylal sodium, and methitural sodium.

Pharmacology.—Although the anesthetic potency of methitural sodium is about two-thirds that of thiopental sodium in the cat, dog, and monkey, equivalent anesthetic doses show that methitural sodium is equally as efficacious as an anesthetic as thiopental sodium or thiamylal sodium and that recovery with methitural sodium was significantly more rapid than with these agents. Cumulative action of methitural sodium was negligible as compared with the older drugs (11–16). There appears to be no synergistic action between atropine, morphine, succinylcholine or *d*-tubocurarine and methitural, so that the usual dosages of these drugs can be used with methitural.

Methitural sodium did not produce salivation or laryngospasm in the monkey, and atropine premedication prevented salivation in cats

and dogs and reduced the incidence of laryngospasm. Reduced muscle tone and transient fall in blood pressure with methitural sodium and thiopental sodium were of almost equal grade (17), but cardiac acceleration was markedly increased in the dog and monkey by thiopental sodium and thiamylal sodium.

Daily administration of methitural sodium for more than a month apparently does not produce tolerance nor cumulative effect. It is reported that no abnormal neurologic or hematologic changes, impairment of liver or kidney function, or gross or significant microscopic pathological changes in the tissues were noted. However, when administered daily by intravenous route to dogs, thiopental sodium produces considerable damage to the liver while methitural sodium in equivalent anesthetic dosage showed only minimal effect (18, 19). Methitural sodium appears to be more rapidly cleared from the plasma than are the other intravenous anesthetics (18).

Clinical Investigation

Methitural sodium was administered to 800 patients in this series. No attempt was made to select these patients and we did not alter the preoperative medication from our usual routine. The patients ranged in age from 7 to 94 years.

We began our investigation using a 10 per cent solution of methitural sodium. A few patients who received this high concentration exhibited evidence of vein irritation which disappeared postoperatively but was considered somewhat annoying. No vein irritation was observed using a 5 per cent solution. However, occasional laryngospasm and some coughing and hiccups were noted. A 0.5 per cent solution of methitural sodium was then employed as a continuous drip with nitrous oxide and oxygen for operative procedures lasting more than one-half hour, and no coughing, laryngospasm or hiccups occurred. Therefore, we believed that these reflexes were not evoked using this concentration. A 2.5 per cent solution of methitural sodium for induction of anesthesia proved satisfactory. Sterile distilled water, normal saline or 5 per cent dextrose in water was used as a solvent.

Dosage.—One hundred twenty-five to 250 mg. of the drug were administered as a preliminary test followed by additional methitural sodium as required. For minor operative procedures (such as, cystoscopies, cauterization of cervices, closed reductions) 500 mg. to 1 Gm. were usually required. Dosage was determined by the response of the patient as recognized by the usual signs relating to intravenous thiobarbiturate anesthesia. As much as 2.5 Gm. of methitural sodium has been administered to individual patients. These patients awakened within thirty minutes without ill effects. Several obstetric patients with eclampsia were controlled with methitural by intravenous drip, and a total of 19 Gm. was administered to one such patient over a 34-hour

period. The baby was delivered in good condition without evidence of significant respiratory depression by cesarean section with the aid of procaine local infiltration.

Preanesthetic Medication.—Preanesthetic medication with scopolamine, 0.43 mg., proved satisfactory. When morphine sulfate, 10 mg., or meperidine, 50 mg., secobarbital sodium, 0.1 Gm., or pentobarbital sodium, 0.1 Gm., was added, induction could be started in the usual time. However, patients in the outpatient department did not receive any medication preoperatively.

Control.—Oxygen was readily available together with facilities for inhalation anesthesia, and equipment for endotracheal intubation. Use of supplemental nitrous oxide and oxygen served to reduce the requirement for methitural sodium in prolonged surgery. Ether, cyclopropane, and oxygen were used also with methitural sodium. When muscular relaxation was desired, *d*-tubocurarine or succinylcholine were employed in this series.

Results

In the outpatient department methitural sodium was given to 26 patients as the sole anesthetic for closed reductions and incisions and drainages. No preoperative medication was administered. Recovery was rapid and complete so that patients were able to go home within thirty minutes.

Methitural sodium was given to 294 surgical patients undergoing all types of surgical procedures where thiobarbiturates were indicated. We used methitural as an induction agent followed by cyclopropane or nitrous oxide and oxygen. Intubation was accomplished with ease using methitural, 500 mg., and succinylcholine, 30 mg. With some of the patients we used *d*-tubocurarine or ether when relaxation was needed. It was observed that a continuous drip of 0.5 per cent or 0.8 per cent solution provided the smoothest anesthetic in our hands.

Four hundred and ninety-four obstetric patients were given methitural in the delivery room, followed by nitrous oxide and oxygen. In some instances when additional relaxation was required, ether was added. These patients were given sodium pentobarbital, Demerol®, or scopolamine, or a combination of these drugs as premedication. The time between the administration of methitural sodium and delivery of the baby varied between two minutes and thirty-five minutes, averaging twelve minutes. The lack of apparent respiratory depression of the newborn, regardless of the elapsed time, was particularly impressive.

Complications.—During induction, brief coughing was noted in 46 of the 800 patients and transient hiccups in 32 patients, although the patients had no postoperative memory of either. These manifestations were virtually eliminated when the 0.5 per cent continuous drip

or the 2.5 per cent solution was used. Eight patients complained of pain in the arm along the course of the vein when a 10 per cent solution was used. This did not occur with the 5 per cent or 2.5 per cent concentrations. Mild laryngospasm was observed in 16 of the 800 patients. These were not severe and passed rapidly. Significant decrease in amplitude and respiratory rate was seldom observed.

Summary

Methitural sodium, a new short acting thiobarbiturate anesthetic, was administered to a series of 800 surgical and obstetric patients with favorable results. The drug exhibited advantages of lowered milligram potency, diminished cumulative effect, and an extremely rapid and complete recovery. Following its use for brief procedures on ambulatory patients, prompt recovery permitted discharge usually within thirty minutes.

Four hundred ninety-four obstetric patients received methitural sodium for delivery. Awakening was extremely prompt, and there were no noticeable depressing effects on the newborn.

Side effects observed in this series of 800 patients included brief coughing in 46, transient hiccups in 32, and mild laryngospasm in 16 patients. These side effects were virtually eliminated by reduction in concentration of the drug from a 10 per cent solution to a 2.5 per cent solution.

References

1. Lundy, J. S., and Tuohy, E. B.: Intravenous Anesthesia, Presented at Proceedings of the International Assembly Interstate Post-Graduate Medical Association of North America, October 12–16, 1936.
2. Beecher, H. K., and Moyer, C. A.: Mechanisms of Respiratory Failure under Barbiturate Anesthesia (Evipal, Pentothal), J. Clin. Invest. **20**: 549 (Sept.) 1941.
3. Adams, R. Charles: Intravenous Anesthesia, New York, Paul B. Hoeber, Inc., 1944.
4. McClure, R. D., Behrmann, V. G., and Hartman, F. W.: Control of Anoxemia during Surgical Anesthesia with Aid of Oxyhemograph, Ann. Surg. **128**: 685 (Oct.) 1948.
5. Brodie, B. B., Bernstein, E., and Mark, L. C.: Role of Body Fat in Limiting Duration of Action of Thiopental, J. Pharmacol. & Exper. Therap. **105**: 421 (Aug.) 1952.
6. American Medical Association, Council on Pharmacy and Chemistry, New and Nonofficial Remedies. Philadelphia, J. B. Lippincott Company, 1955.
7. Scheifley, C. H., and Higgins, G. M.: Effect of Partial Hepatectomy on Action of Certain Barbiturates and Phenylurea Derivative, Am. J. M. Sc. **200**: 264 (Aug.) 1940.
8. Papper, E. M., and Ngai, S. H.: Anesthesiology, New England J. Med. **250**: 1036 (June 17) 1954.
9. Reiffersheid, M., and Dietmann, K.: Vorlaufige experimentelliklinische Untersuchungsergebnisse mit einem neuen kurzwirkenden Barbiturat (Am 109), Deutsche med. Wchnschr. **79**: 638 (April 16) 1954.
10. Dietmann, K.: Uber die moderne Thiobarbiturat-Kurz-Narkose; Weiterer Bericht uber Thiogenal, Deutsche med. Wchnschr. **79**: 1748 (Nov. 19) 1954.
11. Bunka, H.: Zur Frage der Kurznarkose in der Cynakologie, Arztl. Praxis **6**: 2 (Oct.) 1954.
12. Füsslin, H., Kaniak, E., and Wienmers, K.: Klinische Erfahrungen mit dem Ultrakurznarkoticum Thiogenal, Med. Klin. **50**: 37 (Jan. 28) 1955.
13. Jacob, W.: Kurzwirkende Barbiturate in der Bronchoskopie unter besonderer Berucksichtigung des Thiogenals, Thoraxchirurgie **2**: 269 (Oct.) 1954.

14. Ludorf, W., and Schwier, V.: Beitrag zur Kurznarkose mit Thiogenal, Therap. Gegenw. 94: 18 (Jan.) 1955.
15. Paradowski, K.: Eine neue intravenose Kurznarkose, Med. Klin. 49: 1849 (Nov. 12) 1954.
16. Scherer, G.: Erfahrungen mit einem neuen Kurznarkotikum (Thiogenal) Med. Klin. 49: 923 (June 4) 1954.
17. Irwin, S., Stagg, R. D., Dunbar, E., and Govier, W. M.: New Ultra-Short Acting Intravenous Anesthetic, J. Pharmacol. & Exper. Therap. 116: 32 (Jan.) 1956 (abstract).
18. Burlew, R. W.: Personal communication to the author, 1955.
19. Grovier, W. M.: Unpublished data.