NERAVAL SODIUM: A NEW ULTRA-SHORT-ACTING THIOBARBITURATE: PRELIMINARY CLINICAL INVESTIGATIONS

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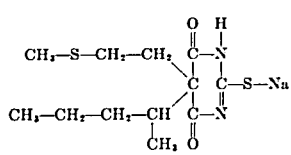
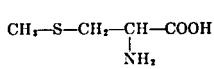
NERAVAL SODIUM (Sch 3132) is the sodium salt of methyl-thio-ethyl-2'-pentyl-thiobarbituric acid. It belongs to the group of ultra-short-acting barbiturates. From a chemical standpoint, this drug is of particular interest because it contains the methyl-thio-ethyl radical ($-CH_2-CH_2-S-CH_3$) present in methionine, the essential amino acid which itself plays a role in detoxification processes. Therefore, the radical mentioned is of great significance in the rapid detoxification and elimination of Neraval, making it the shortest-acting thiobarbiturate so far known to us.

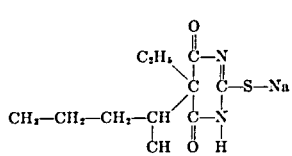
The following formulas demonstrate the relation of Neraval to methionine on one hand and related thiobarbiturates on the other.



Neraval sodium (Sch 3132)



Methionine



Thiopental sodium (Pentothal® Sodium)

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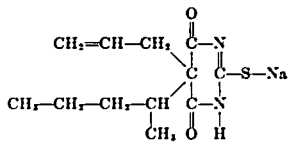

Thiamylal sodium (Surital®)

Neraval crystals have a faint yellow tinge and dissolve slowly in distilled water to form a solution which has a strong sulfurous odor. When freshly prepared, drug concentrations of 2½ per cent and 5 per cent in aqueous solution have a pH of 9.42 and 9.32, respectively. In the same manner as aqueous solutions of other sodium thiobarbiturates, these solutions lose their potency rather rapidly.

Zima, von Werder, and Hotovy (1) summarized their results of experiments with Thiogenal * in animals as follows:

1. Short-acting anesthetic effect with good tolerability.
2. Slight depression of the respiratory center.
3. Quick asymptomatic recovery.
4. Degradation and excretion by way of the liver and the kidneys.

Reifferscheid and Dietmann (2) administered the drug to healthy human beings and concluded that:

1. The average human dosage is about 0.01 Gm./kg. of body weight in order to achieve the sleeping state.
2. The circulation is not influenced to a noticeable degree.
3. In contrast with other ultra-short-acting barbiturates, there is, following a short period of sleep, a definite physical and psychic feeling of well being.

RESULTS OF PRESENT CLINICAL INVESTIGATION

Neraval was used in a manner similar to that preferred for thiopental and thiamylal—that is, intermittent intravenous injections of aqueous solutions in 2½ per cent to 5 per cent concentrations. All cases were supplemented with N_2O in O_2 (50:50 mixtures). Succinylcholine chloride was used when indicated as a muscle relaxant.

The drug was administered to a group of 100 unselected cases which covered a wide range of ages (8 to 83 yrs.) and anesthetic risks. Thirty-five minor and 65 major surgical procedures were performed. The duration of surgery ranged from 10 to 475 minutes. The total amounts of Neraval used varied from a low of 300 mg. to a high of 4,500 mg., averaging an estimated amount approximately 1½ times greater than the amount of thiopental or thiamylal sodium used for similar procedures. Five hundred to 700 mg. of Neraval was required for induction (to achieve the sleeping state), as against 250 to

* Thiogenal is the trademark of Merck-Darmstadt (Germany) for the American product Neraval® made by the Schering Corporation.

500 mg. of thiopental or thiamylal. Induction time (not recorded) seemed considerably slower for Neraval than for thiopental when administered in equal concentration and rate of injection. The incidence of laryngospasm was 3 per cent as against 0 per cent in a series of 100 unselected cases with thiopental anesthesia carried out during the same period of time. Salivation in properly premedicated patients seemed more apparent than with thiopental. In general, cardiovascular effects were similar to those produced by other thiobarbiturates; that is 75 per cent of the patients showed no change during induction. Hypotension was evident during the induction period in 25 per cent of the patients. This was moderate in the normotensive patients (10 to 30 mm. of Hg systolic). There was no significant change in the diastolic level. In hypertensive patients, alterations in blood pressure were more marked, ranging from 30 mm. to 100 mm. of Hg systolic depression and 10 mm. to 30 mm. of Hg diastolic depression. Hypotension coincident with induction improved gradually and there was no further depression that could be attributed to the drug *per se*. There were few accompanying pulse rate changes, though at times a transient bradycardia occurred.

During the maintenance of anesthesia, repeated doses were large in comparison with the amount used when thiopental was the anesthetic agent. Only when it was appreciated that the drug detoxified significantly faster than either thiopental or thiamylal could an even phase of anesthesia be maintained satisfactorily.

The rapidity with which the majority of the patients awoke following anesthesia was striking; 60 per cent were awake in the operating room at the conclusion of surgery and discontinuation of the N_2O—O_2 inhalation; 33 per cent were awake within 37 minutes, 22 per cent of these within 15 minutes; and 8 per cent were unconscious for more than 37 minutes. Five of the latter patients had undergone neurosurgical procedures, and we feel certain that the prolonged narcosis was secondary to the surgical trauma. The other three were prolonged intra-abdominal procedures on poor-risk patients (ages 55, 60, and 83 years). The 83 year old patient was a class III risk who received 4225 mg. of Neraval for a 3-hour subtotal gastric resection. He slept for 90 minutes after anesthesia. In all of these 8 cases, reflex activity was present at the end of anesthesia.

Drug concentrations of over 2½ per cent were quite irritating. The patients complained of pain and a burning sensation along the course of the vein used for injection. Some of these patients complained for 2 to 3 days postoperatively; however, there were no permanent ill effects.

DISCUSSION

A clinical evaluation of the ultra-short-acting thiobarbiturate Neraval sodium (Sch 3132) was made, using a series of 100 unselected

surgical cases. Our clinical findings were consistent with those reported by Zima, von Werder, and Hotovy (1) in animals and Reifferscheid and Dietmann (2) in normal human beings. We were impressed by the rapidity with which this drug is detoxified and by the fast awakening. It takes larger and more frequent doses than one is accustomed to give when this drug is employed in a manner similar to other ultra-short-acting barbiturates.

We recommend this drug when a rapid postoperative awakening is desired; for example, for the ambulatory patient and for those in whom an early stir-up regimen is indicated. The short stay in the recovery room is of advantage to the patient and fewer hours of close nursing supervision are required. In fact, many patients do not have to stay in the recovery room. Although there is apparently more parasympathetic activity than when other barbiturates are used, it is not significant enough to alarm the experienced anesthesiologist. The three cases of laryngospasm were controlled easily by intravenous injections of 10 to 20 mg. of succinylcholine chloride and by positive pressure administration of oxygen. Other undesirable effects, such as hypotension during induction, were of about the same intensity as those seen when other barbiturates were used.

This drug is contraindicated for any patient for whom other barbiturates are contraindicated for general anesthesia.

SUMMARY

1. Neraval sodium, a new ultra-short-acting thiobarbiturate, was used in 100 cases with satisfactory clinical results.

2. The drug appears to have slightly more parasympathomimetic action than other thiobarbiturates but not of any serious consequence.

3. Awakening time is significantly shorter than with other ultra-short-acting thiobarbiturates.

4. There were no serious complications nor any deaths attributable to the drug.

REFERENCES

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2. Reifferscheid, M., and Dietmann, K.: Vorläufige experimentell-klinische Untersuchungsergebnisse mit einem neuen kurzwirkenden Barbiturat (Am 109), Deutsche med. Wchnschr. 79: 638 (April) 1954.