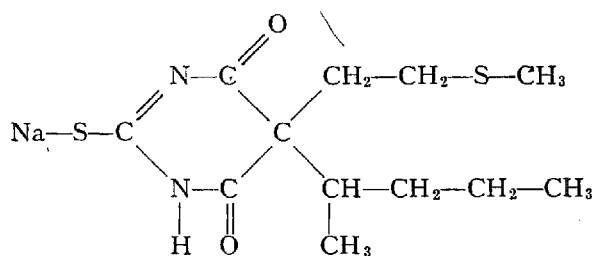


NERAVAL®* (METHITURAL SODIUM) (SCH. 3132)**

JACQUES HOUDE, M.D., F. HUDON, M.D., F.R.C.P.(C), F.F.A.R.C.S.,
and ANDRIÉ JACQUES, M.D., F.R.C.P.(C.)***

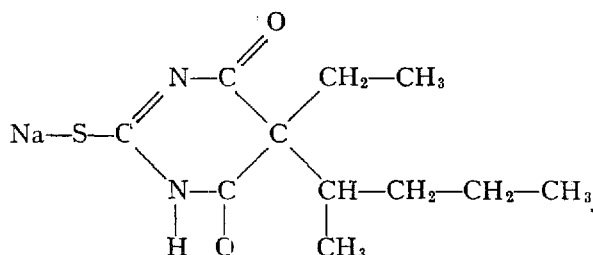
ANAESTHESIA, always in search of progress, has added to its hypnotic arsenal a new drug which seems to compete with the other thiobarbiturates already in use. It is known as Neraval.

Neraval sodium is an intravenous anaesthetic of ultra-short action; it is used in Italy under the name of "Diogenal" (1) and in Germany as "Thiogenal." It differs from the other thiobarbiturates in the fact that it has a second sulphur atom on a special lateral chain methylthioethyl (CH₂-CH₂-S-CH₃).



NERAVAL SODIUM

Methylthioethyl is a radical found in methionine, an essential amino acid playing an important role in the process of detoxification (2). Methionine, moreover, was once used in pre-anaesthetic medication to reduce to the minimum protein catabolism during anaesthesia (3).



PENTOTHAL SODIUM

The presence of the methylthioethyl radical in Neraval sodium explains its ultra-short action; this is due to the rapid destruction and elimination by the liver and kidneys. Thus, methionine would be an agent protecting the functions of the liver.

*Neraval was supplied through the courtesy of the Medical Research Division of Schering Corporation, Bloomfield, New Jersey, U S A

**Paper presented at the meeting of the Canadian Anaesthetists' Society (Quebec Division) May 5, 1956, at Laval Hospital, Quebec, P.Q.

***Department of Anaesthesia, L'Hôtel-Dieu de Québec, Quebec, P.Q.

Neraval is presented in a vial containing two grams of pale yellow crystals. The solution is prepared in the following manner. 2 grams of Neraval are dissolved in 80 cc. of bidistilled water; this gives a 2½ per cent solution. A 5 per cent solution can be used, but a 2½ per cent seems preferable, because with the latter there is less coughing during induction and there is no sensation of pain in the arm during injection.

At the Hôtel-Dieu de Québec, Neraval has been used in 112 cases for patients varying in ages between two and eighty-two years old, in the bad as in the good cases, and in surgery of both long and short duration. We report here clinical observations during the use of methitural sodium.

The intravenous injection of the 2½ per cent solution did not give rise to any local reaction and the patients did not complain of pain in the arm. Moreover, the drug was compatible with the curares usually employed, such as, flaxedil, d-tubocurare, succinylcholine. Neraval was given slowly, because too rapid injection caused coughing or hiccoughs, thus, induction with methitural sodium was slightly slower than with the other thiobarbiturates. Moreover, Neraval having two-thirds the strength of pentothal, the quantity required to produce hypnosis was greater than with pentothal. For an adult of normal stature the required dose for induction was approximately 750 milligrams

There were no laryngospasms or bronchospasms and, moreover, the introduction of an oro-pharyngeal airway did not give rise to any reflexes even at light stages of anaesthesia. Respiratory depression was minimal and much less than that observed during the use of the other thiobarbiturates. Boone *et al* (2) report that Neraval is slightly more parasympathicomimetic than the other barbiturates, but we are not of the same opinion. On the other hand, Irwin, Stagg *et al* (4) state that a pre-medication including atropine diminishes or abolishes salivation and coughing, and seems to increase the depth and duration of the anaesthesia with methitural sodium

As for circulation, methitural sodium drops the systolic blood pressure from between twenty to thirty millimetres of Hg, the diastolic remaining unchanged. With the drop in pressure, there is an acceleration of the pulse which returns quickly to normal while the blood pressure requires more time to reach its previous level. There is also a generalized vaso-dilatation similar to that observed during the use of the other barbiturates. Coloration of the skin remains good and the subjects do not appear intoxicated. Finally, the urticarian erythema often seen on the face, neck and thorax after injection of barbiturates does not appear. As far as surgical haemorrhages are concerned they are no more pronounced than usual, as a matter of fact, they seem to be less.

As far as the central nervous system is concerned, there were no chills, convulsions, mydriasis, or agitation. In a case of curarisation for surgery of the cornea, the patient, who had received a dose of Neraval less than that required to produce hypnosis, remained calm and could answer the questions asked very well.

Neraval being a barbiturate of ultra-short action, it is evident that to maintain the anaesthesia it will be necessary to repeat the administration according to the length of the surgical intervention. The maintenance dosage should be 250 mg., and repeated administration should not be feared because the cumulative effects

of Neraval are less pronounced than with the other thiobarbiturates (4). Moreover, its methylthioethyl radical seems to be a protective agent of the liver functions. Neraval, as previously mentioned, has two-thirds of the strength of pentothal, therefore, to obtain the same anaesthesia the total dosage will have to be greater than that of pentothal. The minimal dose used was 250 mg., and the maximal was 1700 mg. Boone *et al.* (2) have used as much as 4½ grams. As secondary agents, the usual drugs such as curare, demerol, N₂O, and cyclopropane can be used. For surgery of long duration, the possibility of administering Neraval by the drip method should be considered.

At the end of the intervention, recovery is rapid and complete with prompt return of full consciousness. In fact, 82 per cent of the patients in this series woke up on the operating table at the end of surgery and answered questions satisfactorily. This is a great advantage, permitting less congestion of the recovery room, giving the staff more time for the patients who need greater care. The other 18 per cent all woke up half an hour after the end of surgery.

Let us now follow the patients on the wards to discover the reactions following their recovery. First, let us mention that the patients do not stay in a state of hypnosis usually responsible for an amnesia of six to eight hours following a surgical intervention. The patients simply rest, are not nauseated, and vomiting is greatly diminished. Is this due to the methylthioethyl radical or to the less pronounced parasympathicomimetic effect of Neraval?

A few patients who had been previously anaesthetized with pentothal, were questioned following administration of Neraval. All of them declared themselves to be very satisfied and some even admitted their preference for the latter. "It is strange," said one woman, "it is as though I had not been put to sleep at all, feeling as well as I do now." Moreover, a few patients having undergone minor surgery in the morning took a light meal and did not suffer from it, because digestion proceeded as normally as usual. All the patients were up and around on the day of the intervention and none of them complained of vertigo.

The ambulatory patients also benefited from this recent discovery. At the Hôtel-Dieu de Québec, pentothal is never used for out-patients for the simple reason that they take too long to wake up, and for this reason cannot return to their home for many hours following intervention. With the arrival of Neraval, these objections did not occur and so it was used on twelve ambulatory patients. All of these patients left the hospital during the hour following intervention not incommoded by vertigo, nausea or vomiting. Socially speaking, this is a victory considering that most of the people have a certain fear of gas anaesthesia and ask for an intravenous anaesthesia.

The surgical follow-ups were normal with all these patients. Only 5 per cent were nauseated and vomited and in all these cases, the symptoms were of short duration. It is clearly evident that Neraval causes less nausea and vomiting than the other barbiturates and it is to be admitted that this is a great quality in its favour. As far as the lungs and the circulation are concerned, we did not notice any complications and the same can be said of the urinary system. It is to be concluded that Neraval is less toxic and that its rapid elimination makes it an anaesthetic agent of choice.

The use of Neraval is indicated in all cases where barbiturates are in order; these indications are numerous and known. Let us review some of the contraindications. The age factor, it seems, does not enter into the contraindications, because methitural sodium was used very satisfactorily on patients with ages varying between two and eighty-two years. In the young and the old, the other barbiturates have the disadvantage of producing respiratory depression and of prolonging the anaesthesia into the postoperative period. On the other hand, although Neraval depresses respiration, its effect is very slight, and its rapid elimination permits a complete and prompt return to consciousness immediately at the end of the intervention. We did not use any thiobarbiturates in obstetrics or for Caesarean sections, because they seem to be too dangerous for the child, and for this reason they oblige the surgeon, or the obstetrician, to hasten too much in his work. Neraval was used for one case of Caesarean section when the surgeon did not have to hurry and the child was born with a good colour, breathing spontaneously. Finally with the cardiacs and the very sick, it is evident that all the usual precautions have to be taken because even though Neraval is an anaesthetic of choice, this does not mean that it keeps us from all possibility of accident.

In conclusion, ultra-short action, minimal respiratory depression, weak toxicity, rapid elimination, absence of post-surgical accidents, are advantages that permit us to believe that Neraval is an anaesthetic of quality that promises much for the future. What we have said here constitutes only a preliminary report based on a series of 112 cases. Further use will permit us to determine in more detail the properties and particular advantages of this new thiobarbiturate.

REFERENCES

- 1 CALLIGARI, G, & BÉRIO, E Experimentazione clinica di un nuovo barbiturico ad azione ultrabreve nota preliminare. *Minerva anesthesiologica*, 22 2, 70-2 (Feb. 1956)
- 2 BOONE, JOHN D, MUNOZ, RAFAEL & DILLON, J B Neraval Sodium. A New Ultra-short-acting Thiobarbiturate Preliminary Clinical Investigations *Anesthesiology*, 17 2, 284 (March 1956).
- 3 HARRIS, T A B The Mode of Action of Anesthetics, p 497. Edinburgh E S Livingstone Ltd (1951)
- 4 IRWIN, S, STAGG, R D, DUNBAY, E & GOVIER, W M, Schering Corporation, Bloomfield, New Jersey Abstract of Papers, Fall meeting, Iowa City, September 6-8, 1955, Congress American Society for Pharmacology and Experimental Therapeutics *J Pharmacol. & Exper Therap.*, 116. 32 (Jan. 1956).
- 5 Clinica Ortopedica della Università di Siena, Direttore Prof L GIUNTINI Anestesia generale endovenosa ultrabreve in traumatologia C. CHERUBINI *Minerva anesthesiologica*, 22 3, 121-3 (Marzo 1956).