THE CLINICAL USAGE OF NERAVAL*

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DR. HAROLD GRIFFITH, in his address before this meeting one year ago, made the prediction that, within the next ten years, hundreds of new drugs would be produced and tested clinically as anaesthetic agents (1). Today, a short twelve months later, that prophecy already is becoming fact, and a number of these agents have appeared upon the anaesthesiologist's horizon. Among these, there are at least two new ultra-short-acting intravenous barbiturates that, on the basis of available data from laboratory experimentation, warrant further clinical trial and study.

There is a certain justification for the continuing search aimed towards the introduction of a more desirable intravenous anaesthetic agent. The drugs of this type which are presently available have been eminently successful in revolutionizing anaesthetic practices within the past two decades. they have effectively abolished the fear of anaesthesia, and they have made the prolonged, stormy inductions of an earlier day a thing of the past. They have not, however, proved to be ideal drugs on a number of counts These barbiturates often have acted as selective depressants of the medullary centres, particularly the centres controlling respiratory activity and vasomotor tone Respiratory depression and hypotension occasionally have been alarming in degree following administration of these drugs. Furthermore, parasympathomimetic effects have been exhibited which have resulted in such induction complications as coughing, sneezing, laryngospasm, and hiccups; these phenomena, while usually merely annoying, have on other occasions been truly dangerous. Finally, and of most importance, the ultra-short-acting barbiturates have been shown to be, in fact, rather slowly metabolized (2) (3) (4) (5) (6). Convincing evidence has been amassed to demonstrate that the apparently short duration of thiobarbiturate anaesthesia is dependent upon a relatively rapid redistribution of plasma levels of the drug into the fat depots, from which it is slowly liberated and metabolized. Minimal doses thus are of short duration, but larger doses produce prolonged hypnosis. This drawback has intensified the search for a thiobarbiturate that is metabolized more rapidly in the body and will thus permit better control of the anaesthetic state: Neraval Sodium has been suggested as just such a drug.

CHEMISTRY AND PHARMACOLOGY

Neraval Sodium[1] is the sodium salt of methyl-thio-ethyl-2'-pentyl-thiobarbituric acid.

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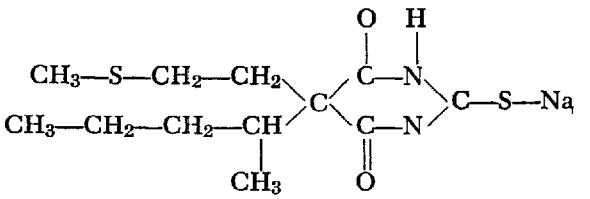
[1]Generous supplies of Neraval Sodium were made available to the authors during these studies by the Schering Corporation, Bloomfield, New Jersey.



The compound is unique among the thiobarbiturates in that it contains two sulphur atoms, there being a methyl-thio-ethyl radical at the 5 carbon atom in addition to the sulphur atom at the 2 carbon position as is found in the more familiar Pentothal and Surital. The relationship of this methyl-thio-ethyl radical to the essential amino acid, methionine, has been commented upon (7), and it has been postulated that the presence of this radical may be of importance in the detoxification process of the drug.

In animals, the intravenous administration of Neraval solution promptly induces an anaesthetic state that is characterized by its brevity and by the rapid recovery period. The intravenous administration of either 40 mgm./kgm. of Neraval or 25 mgm./kgm. of Pentothal produced a similar depth and duration of surgical anaesthesia in the dog, the same was true of 30 mgm./kgm. doses of Neraval and 18 mgm./kgm. doses of Pentothal in the monkey. The anaesthetic potency of Neraval is thus approximately two-thirds that of Pentothal in both species. At these dosage levels, which produced comparable depths and duration of anaesthesia, complete recovery, as estimated by a return to a co-ordinated walk, was significantly more rapid following the administration of Neraval than after anaesthesia produced by Pentothal (8).

Clinical Studies

The clinical usage of Neraval has been studied extensively in Europe, particularly in Germany (9), for the past two years, but interest in the drug is of far more recent origin on this continent (7) (10). The present investigations were based upon 300 clinical administrations of Neraval, and were designed primarily to elucidate the effects upon the functions of the vital medullary centres, to enumerate the incidence of parasympathomimetic complications during the induction period, and to evaluate the recovery time following anaesthesia. All results have been expressed as arithmetic means, and, where practicable, have been subjected to appropriate statistical analysis.

The first phase of investigation consisted of one hundred operations of relatively short duration, dilatation of the cervix and curettage of the uterus, performed on one hundred patients, fifty of whom were anaesthetized with a 2½ per cent solution of Pentothal (the standard ultra-short-acting thiobarbiturate presently in use in the Department of Anesthesiology at the Hartford Hospital), and fifty with 2½ per cent solution of Neraval (Table I). Every effort was employed to produce two comparable series. Only risk one patients, with normal hematocrits, were selected for either series. The ages and weights of the patients in each series were not statistically different: the average age of the patients receiving Pentothal was 40.2 ± 1.60 years, while that of the patients receiving Neraval was 37.5 ± 1.95 years, the average weight of the patients receiving Pentothal was

TABLE I

COMPARISON OF NERAVAL AND PENTOTHAL IN COMPARABLE SERIES OF D AND C'S

	Pentothal 2½%		Neraval 2½%		
Patients	50		50		
Age (years)	40 2	1 60	37 5	1 94	p>0 05
Weight (pounds)	138 0	3 65	133 9	3 35	p>0 05
Induction time (seconds)	75 1	3 46	160 8	9 65	p<0 01
Induction dose (mgm)	252 9	13 34	431.5	23 75	p<0 01
Induction dose (mgm /lb)	1 86	0 079	3 25	0 152	p<0 01

138 0 ± 3.65 pounds, while the average weight of the patients receiving Neraval was 133 9 ± 3.35 pounds. The drugs and doses employed for premedication were approximately the same in each series, and generally consisted of an oral barbiturate (Seconal or Nembutal) two hours prior to the induction of anaesthesia, and the hypodermic administration of an opiate (morphine sulphate or Demerol) one hour before operation All the patients were anaesthetized by a single anaesthesiologist, and the same technique was employed in each instance

The barbiturate drug was injected into the tubing of a free-flowing intravenous infusion at a standard rate of 6 cc. of Pentothal per minute or 12 cc. of Neraval per minute. The induction time was measured in seconds from the beginning of barbiturate injection to the loss of the eyelash reflex, and averaged 75.1 ± 3.46 seconds for Pentothal and 160 8 ± 9 65 seconds for Neraval, a difference that is highly significant from the statistical viewpoint. The difference between the amount of each drug that was required to effect induction also was highly significant on a statistical basis: the average induction dose of Pentothal was 252.9 ± 13.34 mgm., as compared to an average induction dose of 431.5 ± 23 75 mgm. of Neraval. The induction dosage was calculated on a weight basis, and found to average 1.86 ± 0.08 mgm./lb. for Pentothal, and 3.25 ± 0 15 mgm./lb. for Neraval.

The effects of the two drugs upon certain vital functions were evaluated in each series of patients immediately following induction, and are recorded as the

TABLE II

COMPARISON OF NERVAL AND PENTOTHAL IN COMPARABLE SERIES OF D. AND C'S EFFECTS

	Pentothal	Neraval
Blood pressure	– 10 32%	– 12 20%
Pulse rate	– 11.16%	– 12 06%
Respiratory Rate	– 11 14%	– 6 58%

arithmetic mean of the percentage of change from the resting preoperative values (Table II). The systolic blood pressure decreased an average 10.32 per cent following the induction of anaesthesia with Pentothal, and 12.20 per cent

following induction with Neraval. Pulse rate also was decreased by both drugs, the decrease amounting to 11.16 per cent of the pre-operative value following induction with Pentothal and 12.06 per cent following induction with Neraval. The respiratory rate was decreased 11.14 per cent when Pentothal was employed for induction, but only 6 58 per cent when Neraval was the anaesthetic agent. The increased susceptibility of the respiratory apparatus to the effect of Pentothal in comparison to that produced by Neraval also is suggested by the fact that induction doses of Pentothal resulted in apnoea in 3 of the 50 patients, while apnoea occurred in only one of the fifty patients receiving Neraval.

Induction was considered complete following the loss of the eyelash reflex, and nitrous oxide–oxygen, at flow rates of 5.5 and 2.5 litres per minute, were then administered by the semi-closed, circle filter carbon dioxide absorption technique. The need for subsequent intravenous increments of barbiturate was determined by the urgency, depth, and rate of respiration, the tone of the muscles of the fingers, and the occurrence of limb movement: in all instances an attempt was made to maintain as light a plane of anaesthesia as was compatible with the exigencies of the operative procedure (Table III). The total duration

TABLE III

COMPARISON OF NERAVAL AND PENTOTHAL IN COMPARABLE SERIES OF D AND C's DURATION

	Pentothal 2½%	Neraval 2½%	
Anaesthesia time (minutes)	15 7 ± 7 09	19 6 ± 1 27	p>0 05
Total dose (mgm)	429 6 ± 20 0	693 5 ± 25 26	p<0 01
Total dose (mgm /lb)	3 12 ± 0 12	5 26 ± 0 19	p<0 01
Reflex time (from last dose)	12 70 ± 0 93	14 18 ± 0 94	p>0 05
Waking time (from last dose)	28 35 ± 6 94	29 57 ± 2,89	p>0 05

of anaesthesia was not statistically different between the two series, amounting to 15.7 ± 7 09 minutes in the patients receiving Pentothal and 19.6 ± 1.27 minutes in those patients receiving Neraval There was a significant difference in the total dose of each drug required, however, the total dose of Pentothal averaging 429 6 ± 20.0 mgm , and that of Neraval averaging 693 5 ± 25 26 mgm. Calculated on a milligram-per-pound basis, the total dose of Pentothal was 3 12 ± 0.12 mgm /lb., while the total dose of Neraval was 5.26 ± 0 19 mgm./lb.

Reflex time was measured in minutes from the time of administration of the last dose of barbiturate to the time required for the return of reflex activity, such as swallowing, masseter tone, or the eyelash reflex. It averaged 12 70 ± 0.93 minutes following the use of Pentothal, and 14 18 ± 0.94 minutes after anaesthesia produced by Neraval, a difference that is not statistically significant Waking time was measured from the time of administration of the last dose of barbiturate to the moment at which the patient opened her eyes and responded verbally to questions. The waking time following Pentothal anaesthesia averaged 28.35 ± 6.94 minutes, as compared to 29.57 ± 2.89 minutes following Neraval anaesthesia: the difference between these two waking times is not of statistical significance.

A noticeable difference in the frequency of such complications as hiccup, coughing, sneezing, and laryngospasm was noted during the induction of anaesthesia in these two series of patients: they occurred in 8 of the 50 patients anaesthetized by Neraval, but in only one of the 50 patients anaesthetized by Pentothal It was considered possible that the occurrence of these complications might be related to the speed of administration of Neraval, or to the concentration of the drug that was achieved initially in the blood stream and/or tissues (Table IV). The effects of four different concentrations of Neraval upon the incidence of these induction complications were therefore investigated in four groups of patients. Fifty patients were induced slowly with an intravenous infusion of 0.4 per cent Neraval in 5 per cent glucose and water, and only one instance of hiccup was encountered in this series of patients. A total of 180 inductions were

TABLE IV

COMPLICATIONS DURING NERAVAL INDUCTIONS

	0 4%	2 5%	5%	10%
Patients	50	180	50	20
Burning, pain on injection	0	0	3	2
Hiccups	1	11	3	2
Coughing, sneezing	0	3	2	2

effected with 2.5 per cent concentration of Neraval; hiccups occurred in 11 patients, and coughing or sneezing in 3 others. A third group of patients, numbering 50, were induced with 5 per cent concentration of Neraval hiccups were produced in three patients, and coughing or sneezing in two others Three of the patients in this series complained of burning or pain during the administration of Neraval, despite the fact that injections were made into the tubing of a free-flowing intravenous infusion of 5 per cent glucose and water. A final 20 patients were induced with 10 per cent concentration of Neraval: 2 patients complained of burning or pain during injection, 2 more developed coughing or sneezing during induction, and 2 began hiccupping. The hiccups in the latter two patients were extremely severe, in one instance lasting one and a half hours, and forced the curtailment of any further investigation of the use of a 10 per cent concentration of Neraval.

A final group of twenty-six patients was investigated for the purpose of determining the exact duration of action of Neraval in comparison with Pentothal. These patients were undergoing electroshock therapy, and each patient received EST on numerous occasions, frequently on an "every day" or "every other day" basis. An opportunity was therefore afforded for the alternate administration of Neraval and Pentothal to the same patient at the time of successive treatments, each patient serving as his or her own control. All of the patients included in this series received each drug on two or more occasions, and there was a total of 68 administrations of Neraval and 67 administrations of Pentothal to the 26 patients constituting this phase of the study Thus, the effects of the two drugs could be compared on the same patient, and in addition the multiple adminis-

trations of each drug to the same patient served to minimize the experimental errors of observation

No premedication was employed prior to the induction of anaesthesia. Venipuncture was performed, preferably in a vein of the antecubital fossa, with the patient lying supine in bed. The patient was then asked to hold the contralateral arm above the bed, and the injection of 2½ per cent Pentothal at a rate of 1 cc. every five seconds, or 2½ per cent Neraval at a rate of 2 cc. every five seconds, was carried out. All times were measured in seconds, by stopwatch, from the time of the beginning of the injection of the barbiturate (Table V) The induc-

TABLE V

COMPARISON OF NERAVAL AND PENTOTHAL DURING ELECTROSHOCK THERAPY
(All times measured in seconds)

	Pentothal	Neraval	
Induction time	53 8 ± 3 59	118 1 ± 11 02	p<0 01
Sleeping time (end of induction to response)	466 3 ± 18 87	399 1 ± 17 40	p<0 01
Total anaesthesia time (start of induction to response)	520 3 ± 19.72	517 3 ± 16 12	p>0 05

tion time of Pentothal was determined from this zero point to the moment when the arm held in the air dropped to the bed, and averaged 53 8 ± 3 59 seconds. The induction time of Neraval, which was administered at a rate that was twice as fast as that employed for Pentothal, was determined in similar fashion, except that the injection of Neraval was discontinued when a dose had been administered that was twice as large as that required to effect induction in the same patient with Pentothal. This variation in technique was based on the earlier observations of the differences in potencies and induction times between Pentothal and Neraval which were made during the first phase of these investigations, and was introduced to prevent a discrepancy between the comparative doses of the two drugs The induction time following the administration of Neraval averaged 118.1 ± 11 02 seconds, and thus differed to a highly significant degree from the induction time following the administration of Pentothal.

At the end of induction, a standard dose of Anectine, varying from 40 to 60 mgm in accordance with the weight and body build of each individual patient, was administered, and the patient was inflated with oxygen by rhythmic manual compression of a breathing bag attached to a face mask until all muscular fasciculations had ceased. Electroshock was then applied, and artificial ventilation was resumed following the convulsion and maintained for the duration of the apnoeic period. A determined effort was made to avoid either hyper- or hypoventilation. The patient's forearm and hand were then pricked every 15 seconds with a pin until the end-point response occurred, shown by the withdrawal of the hand or arm. Spontaneous respirations always occurred prior to this reaction to stimulation, eliminating the possibility that the time of reaction might coincide with, and indeed be dependent upon, recovery from the effects of the relaxant drug

This experimental method permitted the determination of the total anaesthesia time, measured from the start of induction to the moment at which reaction to stimulation occurred, as well as the determination of the sleeping time, measured from the end of induction to the time of reaction to stimulation. The sleeping time following the administration of Neraval averaged 399.1 ± 17 40 seconds and was significantly shorter in comparison to the average of 466 3 ± 18.87 seconds when Pentothal was the anaesthetic agent. The total anaesthesia time, however, was no different following the use of the two drugs, averaging 520 3 ± 19 72 seconds for Pentothal and 517 3 ± 16 12 seconds for Neraval

Discussion

The results of these studies have served to confirm some of the clinical impressions formed by previous workers regarding the usages of Neraval sodium (7) (10), but have been at variance with other aspects of those opinions on certain points. The induction dose and the total dose of Neraval, both on an absolute and on a milligram-per-pound basis, are greater than for Pentothal, the ratio being 1.7:1. The induction time is more than twice that of Pentothal, even when allowance is made for the greater potency of the latter drug by the more rapid administration of a larger dose of Neraval As one patient phrased it, "It's taking a lot longer to go to sleep than the last time I had Pentothal." In most instances, the longer induction time has been of no clinical importance, but on certain occasions, particularly in agitated patients being anaesthetized for electroshock therapy, the prolonged induction has been a definite disadvantage.

The effect of Neraval upon the medullary centres has followed, in general, the pattern seen when other ultra-short-acting thiobarbiturates are employed for the induction of anaesthesia. The systolic blood pressure has been depressed to a minor extent, amounting to a 10 per cent decrease from the preoperative level, but in no instance did the hypotension become alarming in degree. The pulse rate was often unchanged, but in a number of patients there was a definite tendency towards a mild and transient bradycardia. The respiratory rate was depressed in the majority of the patients receiving Neraval, but to a less extent than when Pentothal was employed for induction.

The parasympathomimetic activity of Neraval has produced a number of induction complications with a much greater frequency than is usually encountered following induction with the other commonly employed thiobarbiturates. The occurrence of hiccups, laryngospasm, and coughing or sneezing is not alarming to the experienced anaesthesiologist (7), but the fact remains that these are not desirable phenomena during the induction of anaesthesia, and their high incidence following the administration of Neraval must be considered a definite disadvantage of the drug This is particularly true when they persist well into the postoperative period, as occurred with one patient who developed hiccups following the use of a 10 per cent solution of Neraval, as cited above The occurrence of parasympathommetic activity seemed to increase proportionately with increase in the concentration of Neraval employed. Concentrations of Neraval greater than 2.5 per cent also were irritating on occasion, causing the

patients to complain of burning and pain at the site of injection and along the course of the vein during the administration of the drug.

The sleeping time following the use of Neraval in a carefully controlled series of patients undergoing electroshock therapy was definitely shorter than that observed in the same patients on other occasions when anaesthesia was produced by Pentothal The total anaesthesia time was the same for both drugs, however, the shorter time following Neraval being offset by the longer induction time required with that drug Observations of reflex and waking time in the less well controlled series of patients undergoing dilatation and curettage showed no significant difference as between the two drugs The use of a continuous infusion of 0 4 per cent Neraval for operations of long duration (one to three hours) suggests the possibility that the hypothecated rapid metabolism of Neraval may be more demonstrable following procedures of greater duration than those studied in these investigations. However, it is the consensus of many investigators that all thiobarbiturates owe their apparent rapid action to a redistribution of the drug from the plasma to fat, and that the search for better intravenous anaesthetic agents should be directed towards compounds other than the thiobarbiturates (11).

Summary

1 The use of Neraval has been studied during the course of 300 clinical administrations

2. The induction time of Neraval is more than twice that of Pentothal.

3. Both the induction dose and the total dose of Neraval are 1 7 times that of Pentothal.

4 The effect of Neraval upon the vital medullary centres is similar to that of other ultra-short-acting thiobarbiturates, although there is suggestive evidence that the drug may be less depressing to the respiratory centre.

5 Parasympathetic activity is occasionally quite marked during induction with Neraval, and is manifested by the occurrence of hiccups, coughing, and sneezing or laryngospasm.

6 Concentrations of Neraval above 2.5 per cent may be irritating to the veins into which the drug is injected.

7 Waking time following a sleeping dose of Neraval is shorter than that following Pentothal.

Résumé

Le neraval sodium est un sel de sodium de l'acide methyl-thio-éthyl-2'-pentyl-thiobarbiturique. Parmi les thiobarbituriques, ce composé est le seul à posséder deux atomes de sulfure, il possède un radical methylthio-ethyl aux cinq atomes de carbone en plus d'une atome de sulfure aux deux positions de carbone comme on les trouve dans les deux produits plus connus: Pentothal et Surital. On a fait des commentaires (7) sur le rapport entre ces radicaux et le principal amino-acide, methionine, et il a été émis comme opinion que ce radical pourrait bien avoir une certaine importance dans la détoxification du produit.

Les auteurs ont fait une étude clinique du Neraval sur 300 malades.

Comparée à celle du pentothal, la vitesse d'induction du neraval est deux fois plus lente. Comparée au pentothal, la dose requise pour l'induction aussi bien que la dose totale équivaut a 1.7. Sur les centres médullaires vitaux, le neraval produit des effets semblables à ceux des thiobarbituriques à action très courte, bien que les auteurs soient portés à croire que ses effets sur le centre respiratoire soient moints dépresseurs Au cours de l'induction avec le neraval, on peut observer occasionnellement une prédominance parasympathique assez marquée: elle se manifeste par le hoquet, la toux, l'éternuement ou le spasme laryngé. A des concentrations supérieures à 2.5 pour cent, le neraval devient irritant pour les veines où on l'injecte A la suite de l'administration d'une dose anesthésique de neraval, le réveil est plus précoce qu'avec le pentothal.

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