A COMPARATIVE STUDY OF METHITURAL (NERAVAL*) AND THIOPENTONE

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In the 24 years which have passed since the first report of its clinical use in anaesthesia,[1] thiopentone has become firmly established as a most valuable drug for intravenous use. Although frequently misused, its virtues and its vices have become well known as a result of world-wide experience. A proper appreciation of its vices, in particular, has allowed thiopentone to be administered safely and satisfactorily to so many patients as to establish it as a standard drug for producing unconsciousness in intravenous anaesthesia.

The fact that the drug has vices has encouraged the search for a barbiturate which would prove superior to thiopentone in clinical use. One of the barbituric-acid derivatives with such a potential is the sodium salt of 5-(2[1]-methylthioethyl)-5-(1-methyl butyl)-2-thiobarbituric acid ('Methitural': 'Neraval') and this report is concerned with our attempts to measure the usefulness of neraval, using thiopentone as a standard.

Neraval is one of the ultra-short-acting barbiturates. Its chemical structure is similar to that of thiopentone except that the 5-ethyl radical in thiopentone is replaced by a methylthioethyl radical. This latter is of interest on 2 counts: firstly it is the radical which occurs in methionine, the essential amino acid which plays a part in detoxification processes in the human body[2] and, secondly, this radical introduces a second sulphur atom into the barbiturate molecule.

On the first count it was hoped that the methylthioethyl radical would lead to quicker detoxification in the body and thus to more rapid recovery from anaesthesia, although it is now generally recognized that the short duration of thiobarbiturate anaesthesia is dependent upon a relatively rapid redistribution of plasma thiobarbiturate into fat, whence it is slowly liberated and metabolized.[3]

On the second count, it should be borne in mind that thiopentone differs from pentobarbitone (Nembutal) only by the addition of a sulphur atom on the 2 position in the barbituric-acid ring. Nembutal can be given by intramuscular injection but thiopentone cannot, because its markedly irritant properties lead to ulceration and abscess formation. It has been suggested that the sulphur atom, rather than the pH of the solution, is responsible for the irritant property of thiopentone. If this were so, it would be of interest to ascertain what action, if any, the second sulphur atom conferred upon the methitural molecule in this respect.

We attempted, by subcutaneous injection into rats and rabbits, and by intra-arterial injection into rabbits, to compare the irritant properties of thiopentone and methitural but our results were equivocal and are therefore not published.

Clinical Studies

In studying the clinical response to neraval and thiopentone the double blind technique was employed. Working under sterile conditions, the drugs were mixed and drawn into syringes which were marked in such a fashion that identification was only possible by the person responsible for the preparation of the solutions. This person did not administer any of the anaesthetics in which the drugs were used, and the several anaesthetists who did use the drugs were not able to identify the drug they were using, since

* The Neraval used in this study was made available by the generosity of Messrs. Scherag (Pty.) Ltd., Johannesburg.

the identifying marks were always being altered from day to day and in any event these anaesthetists were never told what drug they had used in any patient, even after the anaesthetic had been given. This method eliminates the unconscious bias which creeps into clinical studies carried out under less rigidly controlled conditions. The thiopentone was employed as a 2·5% solution (wt./volume) and the neraval as a 5·0% solution (wt./volume). A standard anaesthetic technique was employed for every anaesthetic and information was collected under more than 60 headings, and recorded as it was collected. When all the information had been collected, it was transferred to statistical cards and subjected to analysis. Only those cards which had been properly completed were used in the study. The results with thiopentone have been taken as the standard or control.

The patients were given the usual premedication favoured by the anaesthetist, who did not know that the patient was to be a subject for the test until he began his day's work.

After the needle had been inserted into a suitable vein, a test dose of 2 ml. of the unknown solution was administered and certain information, such as pain at the injection site or distal to the site, sleepiness, blood pressure, respiratory rate and pulse rate, was sought for and recorded. A further dose, judged by the patient's response to the first dose, was then given and anaesthesia continued with nitrous oxide (7 l./min.) and oxygen (2 l./min.) and further doses of the barbiturate. All doses, the times at which they were given, and their effects, were recorded, together with data relevant to the study, particularly blood pressure, pulse and respiratory rates. If it became necessary to supplement with any other drug (e.g. ether, muscle relaxant, etc.) this was recorded, and in fact such cases have not been included in this study.

At the conclusion of the operation the patient was left entirely undisturbed for 5 minutes and spontaneous movement, opening of the eyes or efforts to speak, within this period, were noted. Thereafter the patient was returned to his or her bed and visited once more in the recovery period, if that was possible.

Results

The clinical study covered the administration of neraval to 111 patients and the administration of thiopentone to 77 patients. The records of 19 patients in each group were incomplete and these 38 were discarded. There were thus available for analysis the records of 92 administrations of neraval and 58 administrations of thiopentone. These records covered a wide variety of operations in both sexes and in all age-groups.

In order to reduce bias due to age, sex, weight and operation, records were selected for a group of 62 adult females aged between 20 and 40 years and weighing between 100 and 160 lb. All these patients were subjected to a common operation, namely dilatation of the uterine cervix and curettage of the uterine cavity. None of the anaesthetics lasted longer than 25 minutes and the anaesthetics were given by 13 anaesthetists at random over a period of 18 months. Of these 62 patients, 34 received neraval and 28 received thiopentone. They all received the proportions of nitrous oxide and oxygen as already described and, except for the usual pre-anaesthetic medication with a variety of drugs (always including either atropine or scopolamine) and sometimes the intravenous injection of ergometrine, they received no other drugs of any sort as adjuncts to the anaesthetic. It will be seen from Table I that there is no statistical difference of any significance in the weights and in the duration of anaesthesia of the two groups. The complications during anaesthesia and during recovery suggest that detailed statistical study or more extensive clinical trials are not warranted.

TABLE I. RESULTS OF CLINICAL COMPARISONS

	Neraval	*Thiopentone*
Number of subjects	34	28
Mean weight	127 (±14)* lb.	128 (±19)* lb.
Mean duration of anaes.	15 (±5)* min.	15 (±4)* min.
Mean dose	630 (±200)* mg.	342 (±146)* mg.
Dosage range	300-1,000 mg.	175-900 mg.
Pain at injection site	2	—
Sneezing after anaes.	1	—
Coughing: during anaes.	7 (*a*)	4 (*b*)
during recovery	1	—
Hiccough	4	—
Laryngospasm during anaes.	1 (*c*)	—
Shivering during anaes.	1	—
Retching: during anaes.	1	—
during recovery	1	—
Vomiting: during anaes.	1	—
during recovery	1	2
Respiratory rate:		
increased	11	12
unaltered	9	6
decreased	9	8
both rise and fall	5	2
Pulse rate: increased	11	12
unaltered	5	2
decreased	15	13
both rise and fall	3	1
Systolic blood pressure:		
increased	6	5
unaltered	6	1
lowered by 10-20 mm. Hg.	7	8
lowered by 21-30 mm. Hg.	7	7
lowered by 31-40 mm. Hg.	2 } total 22	2 } Total 21
lowered by 41-50 mm. Hg.	3	3
lowered by over 50 mm. Hg.	3	1
both rise and fall	—	1 (*d*)
Recovery (1st 5 minutes):		
moved spontaneously	11	14
opened eyes	8	9
tried to speak	5	7

* Figures in brackets denote the standard deviation of the mean.
(*a*) Of these 7 patients, 4 had oral airway and 1 of these received topical anaesthesia to mouth.
(*b*) Of these 4 patients, 1 had oral airway.
(*c*) This patient had oral airway and topical anaesthesia.
(*d*) The fall was in the range 10-20 mm. Hg.

The mean gravimetric dose of neraval is almost double that of thiopentone.

Neraval is reported to have half the anaesthetic potency of thiopentone in the rat and approximately two-thirds the anaesthetic activity of thiopentone in the cat, dog and monkey.[4] However, such comparisons are usually made on a mg. per kg. of body-weight basis. If the drug molecule is intact when it exerts its effect upon a cell or cells within the body, it is reasonable to postulate that comparison should be made using equimolar solutions rather than solutions of gravimetric equality. Clark[5] points out that although the weight of drug fixed per cell (in experiments measuring the action of cardiac glucosides, for example) is extremely small, yet the number of molecules fixed per cell is large. He quotes the number of phenol molecules required to kill a single yeast cell as being of the order of 3×10^9 molecules. It seems reasonable, therefore, to accept

that a drug with greater molecular weight (e.g. neraval) must of necessity be given in larger gravimetric doses than a similar drug of smaller molecular weight (e.g. thiopentone). Since the molecular weight of neraval is 17% greater than that of thiopentone, one could postulate that doses of neraval should be of the order of 17% greater than doses of thiopentone, if the drugs are equally potent in man. The marked greater gravimetric dosage suggests that neraval is less active than thiopentone in man as well as in experimental animals.

Requirements of Intravenous Anaesthetic Agent

Thiopentone is not an anaesthetic agent in the way that ether and chloroform are. These latter obtund pain to some degree before loss of consciousness, and reflex movements in response to painful stimuli disappear in light planes of unconsciousness. The converse is found when barbiturates are used as anaesthetic agents and for this reason they should always be supplemented with some other analgesic such as nitrous oxide. To displace thiopentone from its place in anaesthesia any drug must (*a*) possess anaesthetic properties approaching those of the true narcotics, (*b*) be cheaper than thiopentone, (*c*) be as easy to prepare and dispense and administer as thiopentone, and (*d*) have fewer side-effects and complications than thiopentone. In the light of the vast knowledge of the chemistry and pharmacology of the barbiturates which has been accumulated it seems unlikely that such a drug, if it exists, will be a barbituric-acid derivative. From the economic point of view it may be better to spend time and effort on refining the use of existing drugs rather than chasing what may be a chimera.

SUMMARY

A new barbiturate for intravenous anaesthesia, Neraval, has been compared with thiopentone in controlled experimental studies.

The results are inconclusive and do not suggest that neraval is in any way superior to thiopentone.

The requirements governing the development of new agents for intravenous anaesthesia are discussed.

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