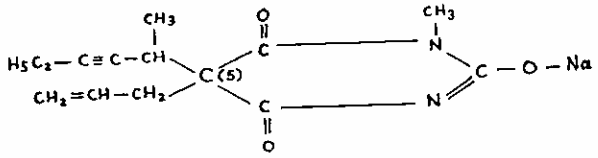
METHOHEXITAL — A NEW INTRAVENOUS BARBITURATE

By George Tay, M.B.,B.S., F.F.A.R.C.S.
(Anaesthetic Department, General Hospital, Singapore)

Although thiopentone sodium has become the most popular induction agent in anaesthesia, it is obvious that it has certain disadvantages, because the search for an "ultra" short-acting barbiturate to replace it still goes on. Thiopentone sodium may have a marked parasympathomimetic effect, and the periods of prolonged basal narcosis following its repeated or even single dose administration may be a disadvantage when dealing with outpatients.

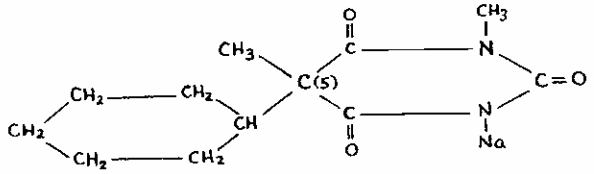
CHEMISTRY AND STRUCTURE — ACTIVITY RELATIONSHIPS

Methohexital sodium is sodium dl- 1 methyl-5-allyl-5- (1-methyl-2 pentynyl) barbiturate, the dl form being the most active of the sterecisomers. Whereas thiopentone is a thiobarbiturate, methohexital is an oxybarbiturate, containing two unsaturated radicles, one acetylenic and one olefinic, attached to the C-5 position.



Methohexital Sodium

It differs from hexobarbitone (Evipan), which is also an oxybarbiturate, in the radicles attached to C-5.

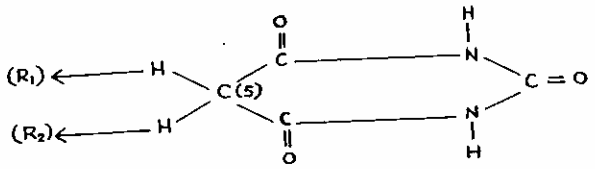


Hexobarbitone Sodium

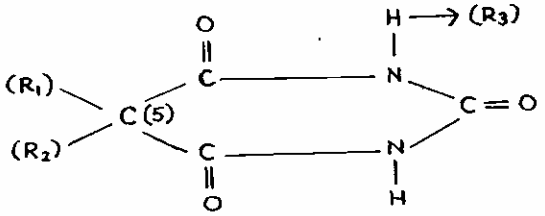
Methohexital is stable in aqueous solution at 25°C. for at least 6 weeks. The pH of a 1% solution is approximately 11.0. It is incompatible with acid solutions such as atropine sulphate and suxamethonium.

A study of the structure-activity relationship of barbiturates (Goodman & Gilman) will reveal the following interesting features:

1. Both the hydrogen atoms on the C-5 position of barbituric acid must be replaced by alkyl or aryl groups in order to obtain compounds with hypnotic properties. An increase in the length of one or both alkyl side-chains (not more than 6 carbon atoms) results in enhanced potency and diminished duration of action.



2. Alkyl groups attached to both the N. atoms yield convulsant compounds, but barbiturates with alkyl groups on only one N. atom show enhanced potency and relatively short duration of action.



3. Compounds with branched side-chains are likely to manifest only brief depressant effects.

4. Unsaturated side-chains tend to result in increased hypnotic activity.

It is easily seen that methohexital sodium satisfies these structure-activity relationships, and we can expect it to be a potent and short-acting barbiturate.

PHARMACOLOGY

Methohexital sodium is about 2½ to 5 times as potent as, and shorter acting than thiopentone sodium. Its shorter duration of action may be due to the fact that it is not predominantly localized in body fats, and its degradation is more complete than thio barbiturates in general. Whereas thiopentone may be parasympathomimetic, methohexital may have a parasympatholytic action and has been used with relative safety in known cases of bronchial asthma.

Being an oxybarbiturate, like hexobarbitone, methohexital is unlikely to cause arterial spasm when injected inadvertently into an artery. This presumption is based on the work done by Burn (1960), showing that thiopentone causes arterial spasm by local release of nor-adrenaline, but that hexobarbitone does not cause spasm. Some wor-

kers (Coleman et al., 1960) have stated that intra-arterial injections of methohexital in calves produced no undesirable response. This deserves further investigation.

CLINICAL APPLICATIONS

Methohexital has been used in 536 cases by the writer, distributed as follows:

General surgery, including thoracotomies, laparotomies and emergencies	303
Gynaecological cases, mainly major procedures	19
Gynaecological outpatients — minor procedures	80
E.N.T. surgery — minor and major procedures	111
Orthopaedic surgery — minor and major	23
Total	536

A 1% solution (1 ml. = 10 mgms.) was used in all the cases, the usual doses being 5 to 10 mgms. per stone body weight. In the majority of cases, only a single induction dose was used, maintenance being with nitrous oxide, oxygen and supplemented by halothane, trichloroethylene, cyclopropane or relaxants when necessary. Supplementary doses of 10 mgms. each time were given where repeated doses were used.

When dealing with induction agents, the presence or absence of certain complications have to be noted. In the main, these are:—

1. Effects on the respiratory system — hiccups, laryngospasm, bronchospasm and respiratory depression.
2. Effects on the cardio-vascular system, mainly hypotension.
3. Excitatory phenomena, such as abnormal muscle movements.

Induction was affected smoothly in the majority of cases, and effects on the respiratory system, as listed above, were not evident. The blood pressure did not show any change in the majority of cases, although a few cases showed transient falls of 10 to 20 mms. mercury systolic. Abnormal muscle movements in the form of jactitations were observed in 12 cases, but these were easily controlled with muscle relaxants.

Recovery was prompt, and more rapid than thiopentone, and post-operative vomiting was noted in only 3 cases, — 2 in which trichloroethylene, and 1 in which cyclopropane were used to supplement nitrous oxide and oxygen.

EVALUATION

Methohexital sodium appears to have certain advantages over thiopentone as an induction agent, in that its actions on the respiratory and cardio-vascular systems are less pronounced than the older established agent. Its shorter duration of action makes it especially suited for minor procedures, like electro-convulsive therapy and the operations carried out on gynaecological outpatients.

REFERENCES

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Goodman, L.S. and Gilman, A. (1958) The pharmacological basis of therapeutics. 2nd. Ed., 5th printing. 125. New York, MacMillan.