SODIUM METHOHEXITAL: A CLINICAL STUDY

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SODIUM METHOHEXITAL (Lilly 25398)² is the high-melting isomer of 1-methyl-5-allyl-5 (1-methyl-2 pentynyl) barbituric acid. It is an ultra-short-acting barbiturate containing no sulphur. The sodium salt is a white powder, readily soluble in water and stable for at least six weeks in an aqueous solution at room temperature. The salt has a pH of 10 to 11. Its properties have been investigated by Redish *et al.* (1) and Stoelting (2). Methohexital has the following chemical formula:

Methohexital was one of seven intravenous anaesthetics previously submitted to comparative investigation in human volunteers (3-4). The evaluation of methohexital in that study was complicated by the fact that all drugs were given in a 2.5 per cent solution, which proved to be too concentrated for methohexital. For this reason and also because it was felt that all the agents studied on volunteers should be investigated clinically as well, the substance was administered under controlled conditions to a series of patients.

METHOD

As in a previous clinical study of methitural (5), administration of the drug was limited to minor gynaecological procedures using only patients in physical status 1 and 2. All patients received oxygen by mask in a semi-closed system at a flow of 6 L./min. Muscle relaxants were given only when relaxation for pelvic examination was inadequate. All patients were premedicated with meperidine 50 mg. and atropine 0.4 mg., intramuscularly.

Anaesthesia was induced with methohexital 1 per cent and maintained with a 0.2 per cent intravenous drip. These concentrations had been found most useful during pilot studies.

Various other concentrations and methods of administration had been tried. However, 2.5 per cent methohexital proved too concentrated. Intermittent in-

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²Supplies of Methohexital were made available in generous quantities through the courtesy of Dr. C. M. Gruber, Jr., Eli Lilly & Company, Indianapolis, Ind., U.S.A.

jection of 1 per cent methohexital is possible, but since the drug is potent and also short-acting, smooth maintenance of anaesthesia was quite difficult. With intermittent injection, depth of anaesthesia fluctuated from deep with apnoea to almost complete wakefulness. Maintenance with a 0.1 per cent intravenous drip was tried, but in some patients it was not possible to maintain smooth anaesthesia with this dilute solution. A 0.2 per cent drip proved the most suitable.

A total of 66 patients were anaesthetized in this series and they were compared with 50 patients in a comparable series who had received thiopental 2.5 per cent following the same premedication. This is the same control series used in the methitural study (5).

DISCUSSION OF RESULTS

Age. The oldest and the youngest patients in both groups have been listed and the mean ages have been calculated in Table I. Statistical analysis failed to reveal any significant difference.

Height and weight. Mean values in the two groups were similar and differences were not significant (Table II). It is, therefore, concluded that the groups were comparable as far as age, height, and weight are concerned.

Time from premedication to induction of anaesthesia. There was a wide variation in the time from premedication to induction from patient to patient (Table III). This is reflected in the means and in the highly significant difference between the two groups. This may have had some influence on the final results, but was unavoidable owing to the uncertainties of an operative schedule.

Duration of anaesthesia and operation. Duration of anaesthesia was the time from induction of anaesthesia to the end of the operation. The longest and the shortest anaesthetic and operating times in each group have been listed (Tables IV and V) and the means for each have been calculated. The average durations of anaesthesia and operation in the thiopental group were significantly greater than in the methohexital group.

Total anaesthetic dose. The difference between thiopental and methohexital was highly significant (Table VI). Almost twice as much thiopental was needed to achieve and maintain anaesthesia.

Induction dose and maintenance dose. The differences between thiopental and methohexital were highly significant, much less methohexital being required for both purposes (Tables VII and VIII).

Dose per minute of anaesthesia. Because of the significant difference in mean duration of anaesthesia in the thiopental group as compared with the methohexital group, the dose required per minute of anaesthesia was determined. This difference was still highly significant (Table IX) and showed that methohexital was one and one-half times as potent as thiopental.

Total sleep time was defined as the time between induction and the patient's purposeful response to verbal command. Both the longest and shortest sleep times were listed for each group, as well as the means (Table X). The difference here was highly significant, which indicates that following a standard operative procedure awakening from methohexital is considerably faster than from thiopental.

TABLE I

AGE

	Oldest	Youngest	Mean	S D	<i>t</i>
Thiopental	69 yr	12 yr	36 yr 3 mo	11 81	0 935 (n s.)
Methohexital	61 yr	18 yr	34 yr 3 mo	11 19	

S D Standard Deviation *t* comparison n s not significant

TABLE II

HEIGHT AND WEIGHT

	Mean height (in.)	S D	<i>t</i>	Mean weight (lb.)	S D	
Thiopental	63 1	2 16	-0 217 (n s.)	136 52	24 48	1 579 (n s.)
Methohexital	63 2	2 76		129 76	20 43	

S D Standard Deviation *t* comparison n s not significant

TABLE III

TIME FROM PREMEDICATION TO INDUCTION

	Longest (hr) (min)		Shortest (min)	Mean (hr) (min)		S D	<i>t</i>
Thiopental	2	49	2	1	20	28 94	-3 189**
Methohexital	3	15	27	1	37 5	29 69	

**Highly significant ($P < 01$) S D Standard Deviation. *t*. comparison

TABLE IV

DURATION OF ANAESTHESIA

	Longest (min)	Shortest (min)	Mean (min) (sec)		S D	<i>t</i>
Thiopental	29	5	18	19	5 42	2 206*
Methohexital	33	5	15	57	6 11	

*Significant ($P < 05$) S D. Standard Deviation *t* comparison

TABLE V

DURATION OF OPERATION

	Longest (min)	Shortest (min)	Mean (min) (sec)		S D	<i>t</i>
Thiopental	27	2	12	40	5 26	2 060*
Methohexital	30	3	10	36	5 43	

*Significant ($P < 05$) S D Standard Deviation *t* comparison

TABLE VI
TOTAL ANAESTHETIC DOSE

	Maximum (mg)	Minimum (mg)	Mean (mg)	S D	<i>t</i>
Thiopental	1,000	250	585.5	146.39	11.122**
Methohexital	510	140	324.8	89.26	

**Highly significant ($P < 0.01$). S.D. Standard Deviation *t* comparisonTABLE VII
INDUCTION DOSE

	Maximum (mg)	Minimum (mg)	Mean (mg)	S D	<i>t</i>
Thiopental	250	75	244	30.12	41.885**
Methohexital	80	35	61.8	7.05	

**Highly significant ($P < 0.01$). S.D. Standard Deviation *t* comparisonTABLE VIII
MAINTENANCE DOSE

	Maximum (mg.)	Minimum (mg)	Mean (mg.)	S D	<i>t</i>
Thiopental	750	0	341.5	147.74	3.318**
Methohexital	450	60	263.0	90.21	

**Highly significant ($P < 0.01$). S.D. Standard Deviation *t* comparisonTABLE IX
DOSE PER MINUTE ANAESTHESIA

	Mean (mg)	S D	<i>t</i>
Thiopental	34.91	15.14	5.121**
Methohexital	22.67	8.71	

**Highly significant ($P < 0.01$). S.D. Standard Deviation *t* comparisonTABLE X
TOTAL SLEEP TIME. INDUCTION TO AWAKE

	Longest (hr) (min)		Shortest (min)	Mean (min) (sec)		S D	<i>t</i>
Thiopental	1	35	9	44	11	21.05	5.143**
Methohexital		48	10	27	40	9.72	

**Highly significant ($P < 0.01$). S.D. Standard Deviation. *t* comparison.

TABLE XI
WAKING TIME FROM LAST INJECTION

	Longest (hr) (min)	Shortest (min.)	Mean (min) (sec)	S D.	<i>t</i>
Thiopental	1 25	7	31 49	18 90	6.367**
Methohexital	45	3	13 17	9 29	

**Highly significant ($P < .01$) S D Standard Deviation *t* comparison

TABLE XII
DOSE PER MINUTE SLEEP TIME

	Mean (mg)	S D	<i>t</i>
Thiopental	15.57	9.72	1.959*
Methohexital	12.67	4.35	

*Significant ($P < .05$) S D Standard Deviation
t comparison

Waking time from last injection was the period from the last injection of thiopental or from the end of the intravenous drip of methohexital until the time when the patient responded to verbal command. Again the difference was statistically significant and confirmed the faster awakening following methohexital (Table XI).

Dose per minute of sleep time. The difference between thiopental and methohexital was significant, thus confirming the greater potency of methohexital (see Table XII).

Side effects (Table XIII). (1) The incidence of *cough* during induction or maintenance with either of the agents was identical and was only of minor clinical significance.

(2) *Hiccough* occurred with sodium thiopental in 12 per cent of the patients whereas it occurred in 41 per cent with methohexital. This difference was highly significant. Whereas hiccough with sodium thiopental was seen on induction only and was never prolonged, with methohexital it persisted on a number of occasions throughout the anaesthesia.

(3) *Movements* occurred in many patients in both groups although less frequently with methohexital than with thiopental. The reason for this high incidence was that slight movements were used as an indication for additional amounts of thiopental or for an increased rate of the methohexital drip. These slight movements may therefore be ignored for purposes of comparison. No disturbing movements other than those indicating the need for more drugs occurred with thiopental anaesthesia (Table XIV). Moderate movements involving the legs to the point where such movements were noticed by the surgeon were classified as moderate. These were not seen with sodium thiopental but

TABLE XIII
SIDE EFFECTS

	Cough			Hiccough			Movements		
	Incidence %	S D	<i>t</i>	Incidence %	S D	<i>t</i>	Incidence %	S D	<i>t</i>
Thiopental	6	03	0	12	05	-3.625**	76	06	2.222*
Methohexital	6	03		41	06		56	06	

*Significant ($P < 0.05$) **Highly significant ($P < 0.01$) S D Standard Deviation *t* comparison

TABLE XIV
SEVERITY OF MOVEMENTS

	None	Slight	Moderate	Severe
Thiopental	12 (24%)	38 (76%)	0	0
Methohexital	29 (44%)	12 (18%)	23 (35%)	2 (3%)

occurred in 35 per cent of the patients who received methohexital. Gross movements involved the entire body and included withdrawal of the pelvis making continuation of the operation difficult and annoying to the surgeon. In two patients such gross movements were seen under methohexital. They could not be entirely controlled by increasing the rate of administration of the drug. On two further occasions anaesthesia could not be maintained with methohexital alone and a change had to be made to inhalation anaesthesia. These two patients were not included in the analysis. One patient who required a rather large amount of methohexital to maintain anaesthesia showed repeated jactitations which were interpreted as preconvulsive movements. Anaesthesia was continued with methohexital, but no true convulsions developed.

Apnoea. The clinical impression that methohexital is a very potent agent and tends to depress respiration has been borne out by the analysis (Table XV). The *incidence* of apnoea following induction with thiopental 2.5 per cent was 94 per cent, whereas that with methohexital is only 56 per cent. This difference was highly significant. On the other hand, the *duration* of apnoea, when it did occur, was markedly longer after methohexital. This difference, however, is statistically not significant because of the great difference in the standard deviation. Nevertheless, the fact remains that when apnoea with methohexital occurs it is likely to be a good deal longer than after equipotent doses of thiopental.

Relaxants. Small doses of succinylcholine were given whenever muscular relaxation was inadequate for proper bimanual pelvic examination. It was needed in 34 per cent of cases under thiopental anaesthesia and in 20 per cent of cases with methohexital anaesthesia (Table XVI). The difference is statistically not significant. One must therefore conclude that muscle relaxation is not a property of either of the two drugs.

Emergence from anaesthesia. Whereas vomiting and retching were relatively common following thiopental anaesthesia, these were seen only once after methohexital (Table XVII). Other minor autonomic disturbances were more common after methohexital. The one case of apnoea on emergence was in a patient who had had prolonged apnoea during anaesthesia but was breathing spontaneously at the end of the operation. This patient was ventilated with oxygen for a short period of time and adequate spontaneous respiration then resumed.

Recovery period. The incidence of post-anaesthetic drowsiness, tiredness and dizziness was small and identical for both agents (Table XVIII). Headache and nausea occurred in one patient following methohexital and one further patient developed unexplained hypotension, which resolved spontaneously.

TABLE XV
APNOEA

	Incidence	S.D	<i>t</i>	Longest (min)	Shortest (sec)	Mean (sec)	S D	<i>t</i>
Thiopental	94% (47)	03	5 428**	2	10	40 1	25 90	
Methohexital	56% (37)	06		18	10	63 5	169 81	-1 102 (n s)

**Highly significant ($P < 01$) S.D : Standard Deviation n s : not significant. *t*· comparison.

TABLE XVI

RELAXANTS

	Mean	S D	<i>t</i>
Thiopental	34% (17)	07	1 750 (n s)
Methohexital	20% (13)	05	

S D.. Standard Deviation *t* comparison n s not significant

TABLE XVII

EMERGENCE FROM ANAESTHESIA

	Depression and drowsiness	Dizziness	Coughing	Hiccough	Vomiting and retching	Shivering	Apnoea
Thiopental	1	1			5		
Methohexital		1	1	1	1	1	1

TABLE XVIII

RECOVERY PERIOD

	Drowsiness and Tiredness	Headache	Dizziness	Nausea	Hypotension
Thiopental	1		2		
Methohexital	1	1	2	1	1

SUMMARY

Methohexital is the only intravenous anaesthetic agent tested by us so far which combines shorter action with a higher potency than thiopental. If dose per minute of anaesthesia for a standard procedure is taken as an indication, the relative potency of thiopental to methohexital is 1:1.54. Nevertheless, the ratio of total sleep time per minute of anaesthesia for thiopental and methohexital is 1:0.7.

Whereas apnoea following induction with sodium thiopental is a fairly constant phenomenon, it is less consistently seen after methohexital but tends to be a good deal more prolonged when it does occur. Induction with methohexital is slow. Not infrequently the patient remains conscious for as long as 10-15 sec. following injection of the drug. Therefore, one may be tempted to make a further injection on the assumption that the first dose had been inadequate. The second injection, however, may well have been unnecessary, and results in prolonged apnoea. As experience is gained in the use of this agent, such prolonged apnoea can usually be prevented. Unfortunately, this makes the agent a potentially more dangerous drug in the hands of the inexperienced. Persistent hiccough is a rather frequent feature of methohexital anaesthesia but is on the whole not too disturbing and terminates spontaneously at the end of anaesthesia. Jactitations were seen once in our series. They have also been observed by others (1).

The intermittent administration of methohexital has been found unsuitable. The high potency combined with very short duration of the drug makes it almost impossible to maintain smooth anaesthesia without causing either prolonged apnoea or awakening. Administration by a continuous intravenous drip is almost mandatory for any procedure lasting more than a very few minutes. This renders the administration of methohexital somewhat cumbersome for the short procedures for which it is most useful. It must, of course, be realized that an intravenous anaesthetic as the sole agent is not ideal, and that this type of anaesthesia was only used in this study to obtain valid comparisons. Some of the objections to methohexital may well not apply if it is used as an induction agent and thereafter only as a supplement to nitrous oxide maintenance. Patients were more awake and less disoriented after methohexital anaesthesia. The incidence of untoward emergence and recovery phenomena was no higher. Muscle relaxation for such procedures as bimanual pelvic examination was not always satisfactory and had then to be provided by succinylcholine. In this respect, methohexital is similar to sodium thiopental. The period elapsing between premedication and induction of anaesthesia was significantly different in the two groups; it is difficult to evaluate the importance of this factor upon the final statistical results.

ACKNOWLEDGMENTS

Statistics were done by Dr. N. Shklov, Department of Mathematics, University of Saskatchewan. The authors are indebted to the members of the Department of Obstetrics and Gynaecology, whose patients were used for this study. Dr. J. H. Harland of the Department of Anaesthesia assisted with the manuscript.

RÉSUMÉ

Nous avons étudié, chez 50 malades qui devaient subir des opérations gynécologiques mineures les effets cliniques du methohexital, un barbiturique non sulfuré à action très courte. Nous avons comparé ces malades à une série de malades semblables à qui on a donné du thiopental. Pour l'induction, le methohexital a été injecté en solution à 1% et, pour le maintien de l'anesthésie, en goutte-à-goutte intraveineux en solution à 0.2%. Nous avons fait inhaler de l'oxygène en circuit semi-fermé à un débit de 6 litres/min.

Nous avons constaté que le methohexital est un médicament très puissant et à action courte. Quand on emploie le methohexital, l'induction de l'anesthésie est lente et il faut faire attention de ne pas injecter une dose additionnelle de médicament avant d'avoir l'effet total de la première dose, car il pourrait s'ensuivre une apnée prolongée. Dans la plupart des cas, l'induction de l'anesthésie est douce à part l'apparition fréquente d'un hoquet tenace. Nous avons été témoins d'un seul cas d'agitation. Nous n'avons pas toujours obtenu un relâchement musculaire suffisant pour permettre un examen bimanuel du bassin ce qui peut être comparé au thiopental à ce point de vue. Après le methohexital, les malades sont plus complètement réveillés et moins désorientés. Il est difficile d'administrer le methohexital de façon intermittente car il est presque impossible de maintenir

un niveau égal d'anesthésie à cause de l'action brève et du grand pouvoir du médicament.

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