SODIUM METHITURAL: A CLINICAL STUDY¹

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SODIUM METHITURAL (Neraval®)⁴ is one of a number of recently introduced ultra short-acting intravenous anaesthetics. Unlike other thiobarbiturates, it has on one of its side chains a second sulphur atom in the form of a thiomethyl group. This is said to accelerate the detoxification of many types of drug (1). The structural formula of methitural is

FIGURE 1

The agent has been under investigation for over two years, and has been commercially available for one year. Its chemical and clinical properties have been described in many previous communications and reference should be made to these for details of chemistry and pharmacology (1-11)

Sodium methitural having been submitted to a comparative study in human volunteers (12, 13), it was decided to evaluate its clinical properties under operating room conditions and again compare the drug with the standard intravenous barbiturate—sodium thiopental.

METHOD

In order to exclude as many variables as possible, the study was limited to minor gynaecological procedures such as D & C, biopsy of cervix, etc., only patients in physical status I and II (classification of the American Society of Anesthesiologists) were included and all administrations and evaluations were done by the authors themselves. The agents were given in freshly prepared 2.5 per cent solutions by the intermittent injection technique. Additional amounts of each drug were administered when signs of too light a level of anaesthesia

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appeared clinically. All patients received oxygen by mask in a semi-closed system at a flow of 6 litres/min.; no other anaesthetics were administered. Muscle relaxants were given only when relaxation for pelvic examination proved inadequate. Injections were made into the median cubital vein and as far as possible at a standard rate of 25 mg/sec. for induction

The premedicated series received meperidine 50 mg and atropine 0.4 mg. intramuscularly. Atropine 0.4 mg. was given to the "no premedication" series. The drugs were given intravenously and in reduced doses when there was not time for the intramuscular route to be effective

Both experimental and commercial methitural were tested since it had been the clinical impression of some investigators that the two had slightly different properties. In the study 42 cases of anaesthesia by experimental methitural without premedication and 57 by the commercial material without premedication were available for analysis. In a further 50 cases, commercial methitural was used with the premedication mentioned above, in another 50 cases sodium thiopental 2.5 per cent was used with premedication

DISCUSSION OF RESULTS

The following comparisons were made (A) thiopental with premedication and commercial methitural with premedication, (B) commercial methitural with premedication and commercial methitural without premedication (this analysis should clarify the influence of premedication upon methitural anaesthesia); and (C) commercial methitural without premedication and experimental methitural without premedication.

Since many early publications were based on experiences with the experimental material, these would have to be reinterpreted if the present study should reveal significant differences between experimental and commercial methitural.

Age (Table I)

TABLE I

		Oldest (yrs)	Youngest (yrs)	Mean (yrs) (mo)		S.D.	†
Thiopental c	(50)	69	12	36	3	11.81	A 0.677 B 0.258 C 0.692
Methitural c	(50)	72	16	34	9	10.90	
Methitural s	(57)	75	13	34	2	11.74	
Methitural (exp) s	(42)	50	19	32	10	7.89	

*Significant ($P < .05$)

**Highly significant ($P < .01$)

S.D. Standard Deviation

† Comparison

The oldest and the youngest patient in each group has been listed, as has the mean age for each group. Statistical analysis of the three standard comparisons A, B and C failed to reveal any significant differences.

Height and Weight (Table II)

Again mean values in these groups were very similar and differences in comparisons A, B and C were not significant. Hence, these four groups were comparable as far as age, height and weight are concerned

TABLE II

		Mean height (in)		†	Mean weight (lbs)		†
			S D			S D	
Thiopental c	(50)	63 10	2 16	A 0 B-1 647 C-0 339	136.52	24 48	A-1 211 B-0 199 C-0 070
Methitural c	(50)	63 10	2 31		129 69	23 64	
Methitural s	(57)	63 94	2 98		128 88	17 42	
Methitural (exp) s	(42)	63 75	2 55		128 61	20 12	

*Significant ($P < .05$)

**Highly significant ($P < .01$)

S D Standard Deviation

† Comparison

Time from Premedication to Induction of Anaesthesia (Table III)

Although in each group there was a large difference in the time from premedication to induction, the means in each group were fairly close. As every anaesthetist knows, it is almost impossible to standardize this particular variable even within reasonable limits because of the uncertainties of the operative schedule. The differences in comparisons A, B and C are not significant. We may therefore assume that the time of premedication did not influence the various aspects of the present study.

TABLE III

		Longest (hr) (min)		Shortest (min)	Mean (hr) (min)		S D	†
Thiopental c	(50)	2	49	2	1	20	28 94	A-0 806 B 1 513 C 1 094
Methitural c	(50)	3	20	34	1	25	29 58	
Methitural s	(57)	1	50	2	1	15	38 10	
Methitural (exp) s	(42)	3	10	5	1	7½	40 77	

*Significant ($P < .05$)

**Highly significant ($P < .01$)

S D Standard Deviation

† Comparison

Duration of Anaesthesia (Table IV)

The time from induction of anaesthesia to the end of operation was noted. The longest and the shortest anaesthetic in each group has been listed and the mean for each calculated. The average duration in the thiopental group was significantly longer than that in the methitural group with premedication (comparison A). This may have been a purely fortuitous finding or an expression of the better operating conditions provided by thiopental. No such differences existed in comparisons B and C.

TABLE IV

		Longest	Shortest	Mean		S.D.	
		(min.)	(min.)	(min.)	(sec.)		
Thiopental c	(50)	29 min.	5	18	19	5.42	A 3.284**
Methitural c	(50)	28 min.	4	15	2½	4.49	
Methitural s	(57)	39 min.	5	15	55	5.97	B-0.865
Methitural (exp.) s	(42)	1 hr. 5 min.	4	18	20	10.72	C-1.316

*Significant ($P < .05$)

**Highly significant ($P < .01$)

S.D.: Standard Deviation

†: Comparison

Duration of Operation (Table V)

The duration of anaesthesia being determined by the duration of the operation, it was not surprising to find that the duration of operation in the thiopental group was again significantly longer than that in the methitural group with premedication and that differences in comparisons B and C were once more not significant.

TABLE V

		Longest	Shortest	Mean		S.D.	†
		(min.)	(min.)	(min.)	(sec.)		
Thiopental c	(50)	27	2	12	66	5.26	A 3.088**
Methitural c	(50)	23	4	9	69	4.26	
Methitural s	(57)	33	1	8	76	5.41	B 0.990
Methitural (exp.) s	(42)	37	1	10	52	8.08	C-1.224

*Significant ($P < .05$)

**Highly significant ($P < .01$)

S.D.: Standard Deviation

†: Comparison

Total Anaesthetic Dose (Table VI)

Here all three differences were significant. In comparison A, this was an expression of the greater anaesthetic potency of thiopental as compared with methitural. Thiopental was almost twice as potent milligram for milligram when

TABLE VI

		Maximum	Minimum	Mean	S.D.	
		(mg.)	(mg.)	(mg.)		
Thiopental c	(50)	1000	250	585.5	146.39	A-12.183**
Methitural c	(50)	1500	625	1021	206.50	
Methitural s	(57)	1750	600	1143	272.25	B- 2.635**
Methitural (exp.) s	(42)	2500	625	1348	370.24	C- 3.158**

*Significant ($P < .05$)

**Highly significant ($P < .01$)

S.D.: Standard Deviation

†: Comparison

comparable operating conditions were provided. Comparison B confirmed a fact well known to all anaesthetists, namely, that preoperative medication will significantly reduce the amount of a general anaesthetic subsequently required. Comparison C indicated that the commercial product of methitural was slightly more potent than the experimental material, this may have been an expression of the greater chemical purity of the newer product.

Induction Dose and Maintenance Dose (Tables VII and VIII)

Again differences in comparisons A, B and C of the means were significant. The reasons for this were the same as those discussed for total dose.

TABLE VII

		Maximum (mg)	Minimum (mg)	Mean (mg)	S D	†
Thiopental c	(50)	250	75	244	30.12	A-21.933**
Methitural c	(50)	500	375	385	34.26	B-2.649**
Methitural s	(57)	625	375	410	61.39	C-2.097*
Methitural (exp) s	(42)	500	375	393	238.41	

*Significant ($P < 0.05$)

**Highly significant ($P < 0.01$)

S D Standard Deviation

† Comparison

TABLE VIII

		Maximum (mg)	Minimum (mg)	Mean (mg)	S D	†
Thiopental c	(50)	750	0	341.5	147.74	A-8.192**
Methitural c	(50)	1,125	250	636	206.84	B-2.117*
Methitural s	(57)	1,375	225	733	266.66	C-3.499**
Methitural (exp) s	(42)	2,000	250	964	360.52	

*Significant ($P < 0.05$)

**Highly significant ($P < 0.01$)

S D Standard Deviation

† Comparison

Dose per Minute of Anaesthesia (Table IX)

Because of the significant difference in mean duration of anaesthesia in the thiopental group as compared with the methitural group with premedication, it seemed advisable to determine the dose required per minute of anaesthesia in order to eliminate any error introduced by this discrepancy of duration. Comparison A between thiopental and methitural with premedication still showed a significant difference. This was to be expected since the average total anaesthetic dose of thiopental was much less than that of methitural for operations which were on the average longer. Thiopental was therefore more than twice as potent as methitural. Although comparisons B and C were no longer significantly

different, it was still interesting that, on the average, less methitural was used when its administration followed premedication than when atropine only was given and that on the average more of the experimental material was needed than of the commercial material, confirming the preceding observations.

TABLE IX

		Mean (mg)	S.D	†
Thiopental c	(50)	34.91	15.14	A-10.384** B- 1.311 C- 1.556
Methitural c	(50)	72.25	20.43	
Methitural s	(57)	78.07	25.46	
Methitural (exp) s	(42)	87.42	32.28	

*Significant ($P < 0.05$)

**Highly significant ($P < 0.01$)

S.D. Standard Deviation

† Comparison

Total Sleep Time (Table X)

This was determined 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. Analysis of comparisons A, B and C failed to reveal significant differences between them. It has been claimed that sodium methitural is a shorter acting agent than thiopental, our findings have shown that, for comparable depth of anaesthesia in a standard operative procedure, no such difference exists between thiopental and methitural.

TABLE X

		Longest (hr) (min)		Shortest (min)	Mean (min) (sec)		S.D.	†
Thiopental c	(50)	1	35	9	44	11	21.05	A 1.155 B-0.740 C-0.711
Methitural c	(50)	1	10	23	40	12	12.24	
Methitural s	(57)	1	55	14	42	24	18.24	
Methitural (exp) s	(42)	1	27	7	45	9	19.48	

*Significant ($P < 0.05$)

**Highly significant ($P < 0.01$)

S.D. Standard Deviation

† Comparison

Waking Time from Last Injection (Table XI)

This was the period from the last injection until the time when the patient obeyed simple verbal commands. Again no statistical difference was demonstrated for the means of comparisons A, B and C. The implications of this were the same as those discussed under total sleep time. Whether a difference of waking exists after shorter procedures not exceeding five minutes remains a matter of speculation.

TABLE XI

		Longest (hr.) (min)		Shortest (min)	Mean (min.) (sec.)		S.D.	†
Thiopental c	(50)	1	25	7	31	49	18.90	A-0.436 B-0.165 C-0.146
Methitural c	(50)		55	9	30	28	11.34	
Methitural s	(57)	1	46	10	30	54	15.69	
Methitural (exp) s	(42)	1	7	4	31	21	15.49	

*Significant ($P < .05$)**Highly significant ($P < .01$)

S D Standard Deviation

† Comparison

Dose/Minute Sleep Time (Table XII)

This relationship shed some additional light upon comparative potencies. Differences in comparisons A and B of the means were highly significant, which again confirmed the greater potency of thiopental and that less anaesthetic drug was needed in the presence of premedication. No significant difference could be demonstrated between experimental and commercial methitural when both were used after atropine premedication only.

TABLE XII

		Mean (mg)	S D	†
Thiopental c	(50)	15.57	9.72	A-6.709** B-4.387** C-0.525
Methitural c	(50)	26.97	7.05	
Methitural s	(57)	34.12	9.73	
Methitural (exp) s	(42)	35.82	19.29	

*Significant ($P < .05$)**Highly significant ($P < .01$)

S D Standard Deviation

† Comparison

Side-Effects (Table XIII)

(1) The significantly higher incidence of *cough* (comparison A) during induction of methitural anaesthesia was striking. Cough was present in only 6 per cent of the patients under sodium thiopental with premedication. Although the difference in comparison B was not significant, it must be noted that the incidence of cough with sodium methitural was greater without than with premedication. Although it had been a clinical impression that cough was less frequent with the commercial than with the experimental product this was not borne out by the final figures.

(2) *Hiccoughs* occurred with sodium thiopental in 12 per cent of cases. Although the difference as shown by comparison A was not significant, the incidence with methitural was nevertheless double that with thiopental. Also hiccough with methitural often persisted throughout the operation. In the series of methitural without premedication however, the incidence was increased to

the point where the difference in comparison B became significant. Premedication therefore reduced the incidence of hiccough under methitural. The experimental material showed a lower incidence of hiccough than commercial methitural, but the difference was not significant.

TABLE XIII

		Cough				Hiccough				Movements		
		Inci- dence (%)	S.D	†		Inci- dence (%)	S D	†		Inci- dence (%)	S.D.	†
Thiopental c	(50)	6	.03	A-2 366** B-1 176 C 0 856		12	05	A-1.581 B-2.472* C 1.515		76	.06	A-1 282 B 0 C-1 131
Methitural c	(50)	22	06			24	06			86	05	
Methitural s	(57)	31.5	06			45.6	07			85.9	.05	
Methitural (exp.) s	(42)	23.8	.07			31	07			93	01	

*Significant ($P < 0.05$)

**Highly significant ($P < 0.01$)

S D Standard Deviation

†: Comparison

(3) *Movements* occurred in very many patients in all four groups and comparisons A, B and C were not significant. The reason for this high incidence was that slight movements were taken as an indication for additional amounts of drug. Therefore, they could not be attributed to the anaesthetic but rather to inadequate depth of anaesthesia. They were always easily controlled by further injections and were often unnoticed by the surgeon. Movements involving the legs to the point where they were noticed by the surgeon were classified as moderate. These movements could not always be entirely controlled by further injections. Gross movements involved the entire body and included withdrawal of the pelvis making continuation of the operation difficult and annoying to the surgeon (Table XIV)

TABLE XIV

		None	Slight	Moderate	Severe
Thiopental c	(50)	12 (24%)	38 (76%)	0	0
Methitural c	(50)	7 (14%)	34 (68%)	5 (10%)	4 (8%)
Methitural s	(57)	8 (14%)	32 (56%)	10 (17.5%)	7 (12.5%)
Methitural (exp.) s	(42)	3 (7%)	24 (57%)	11 (26.5%)	4 (9.5%)

No disturbing movements other than those indicating the need for more drug occurred under thiopental anaesthesia. Moderate and gross movements were seen more frequently when methitural was not preceded by premedication than when it had been given. On three occasions, anaesthesia could not be maintained with methitural and a change had to be made to nitrous oxide and trichlorethylene. These cases were not included in the analyses. There was little if any difference between the experimental and the commercial material in these respects.

It was realized that repeated injection was not necessarily the most desirable

technique for sodium methitural which might have applications in anaesthesia other than as the sole agent for maintenance of anaesthesia. Indeed we rarely ever use sodium thiopental in this way

Apnoea (Table XV)

The clinical impression that sodium thiopental depressed respiration more than sodium methitural has been borne out. The difference in comparison A was significant for both the higher incidence and the longer duration of apnoea following sodium thiopental induction, the incidence being as high as 94 per cent. There was no significant difference between methitural with and without premedication although numerically the incidence was higher when premedication was not used.

TABLE XV

		Incidence	S D	†	Duration		Mean	S D	†
					Long-est	Short-est			
Thiopental c	(50)	94% (47)	.03	A 4 622** B-1 304 C 1.093	2'	10"	40 1"	25 90	A 3 808** B-0 813 C-1 886
Methitural c	(50)	58% (29)	.07		70"	1"	21 2"	23 62	
Methitural s	(57)	70% (40)	.06		90"	5"	24.9"	23 23	
Methitural (exp) s	(42)	60% (25)	.08		6'	5"	16 7"	20 05	

*Significant ($P < .05$)

**Highly significant ($P < .01$)

S D . Standard Deviation

† Comparison

Relaxants (Table XVI)

Relaxants, usually small doses of succinylcholine, were given whenever muscular relaxation was inadequate for proper bimanual pelvic examination. Whereas they were rarely needed when methitural was being used, and then usually only in those patients who were moving vigorously or were coughing, they had to be used rather frequently in the patients receiving smooth sodium thiopental anaesthesia. The incidence of 34 per cent for sodium thiopental is striking and the difference in comparison A with sodium methitural was significant. Sodium methitural, then, had slight relaxant properties. This relaxation would not have been adequate for abdominal operations but was enough to allow a thorough and unimpeded pelvic palpation.

TABLE XVI

			S D	†
Thiopental c	(50)	34% (17)	07	A 3 377** B 0 196 C 0 417
Methitural c	(50)	8% (4)	04	
Methitural s	(57)	7% (5)	03	
Methitural (exp) s	(42)	5% (2)	03	

*Significant ($P < .05$)

**Highly significant ($P < .01$)

S.D. . Standard Deviation

†: Comparison

Emergence from Anaesthesia (Table XVII)

Emergence from anaesthesia usually was quite smooth after both thiopental and methitural. However, hiccough was prominent following methitural and coughing was occasionally encountered. Restlessness was relatively more common in the unpremedicated group. Vomiting and retching were seen after both agents, with a somewhat smaller incidence following methitural with premedication. Most patients were more quickly orientated following methitural than following thiopental.

TABLE XVII

		Depression and drowsiness	Restlessness	Euphoria	Dizziness	Coughing	Hiccough	Vomiting and retching	Diplopia	Bradycardia
Thiopental c	(50)	1	—	—	1	—	—	5	—	—
Methitural c	(50)	1	1	—	—	1	6	2	—	—
Methitural s	(57)	—	4	4	—	—	4	4	—	1
Methitural (exp) s	(42)	1	5	1	—	2	4	6	2	—

Postoperative Period (Table XVIII)

There was little difference between thiopental and methitural with premedication. There were more undesirable side-effects when methitural was given without premedication

TABLE XVIII

		Mental depression	Euphoria	Drowsiness and tiredness	Headache	Dizziness	Diplopia	Inability to focus	Nausea and emesis
Thiopental c	(50)	—	—	1	—	2	—	—	—
Methitural c	(50)	—	—	3	—	2	—	—	—
Methitural s	(57)	—	1	3	1	7	2	4	5
Methitural (exp) s	(42)	1	—	—	—	4	1	—	6

SUMMARY

The properties of methitural with and without premedication have been compared in a series of patients in physical status I and II and of comparable age, height and weight, undergoing minor gynaecological procedures.

Sodium thiopental was approximately twice as potent as sodium methitural, and for comparable depth and duration of anaesthesia, the waking period after methitural was the same as that following thiopental.

The incidence of cough and hiccough was greater under methitural anaesthesia. Hiccoughs, when they occurred, tended to persist throughout the procedure and were also seen in the emergence period. Gross movements were seen only with methitural. Patients were more widely awake and less disorientated after methitural anaesthesia, but showed a higher incidence of nausea and vomiting. The apnoea following an induction dose of methitural was on the average of shorter duration than that following sodium thiopental and its incidence was lower. Muscle relaxation for such procedures as bimanual pelvic examination was more often satisfactory with methitural anaesthesia.

Preoperative medication reduced the amount of methitural required to maintain anaesthesia and decreased the incidence of side-effects.

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RÉSUMÉ

Nous avons étudié les propriétés du méthitural avec et sans prémédication chez un certain nombre de malades dont l'état physique était classifié I ou II, à peu près du même âge, du même poids et de la même taille, malades qui devaient subir des interventions gynécologiques mineures.

Le thiopental sodium était environ deux fois plus puissant que la methitural à profondeur et durée égales d'anesthésie, le réveil avec les deux médicaments survenait dans le même délai.

La toux et le hoquet survenaient plus fréquemment avec le methitural. Quand un malade faisait du hoquet, il avait tendance à en faire durant toute l'opération et même au réveil. On a observé des mouvements importants seulement avec le methitural.

Les malades ont semblé plus complètement réveillés et moins désorientés après l'anesthésie au méthitural mais les nausées et vomissements ont été plus fréquents.

L'apnée, à la suite de la dose d'induction, a duré moins longtemps avec le methitural qu'avec le thiopental et elle est apparue moins souvent. Pour des manœuvres comme un examen bimanuel du bassin, le relâchement musculaire nous a semblé plus satisfaisant avec le méthitural.

Une prémédication a pour effet de diminuer la quantité de méthitural nécessaire pour maintenir l'anesthésie et diminuer aussi l'apparition des effets indésirables.

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