A CLINICAL COMPARISON OF SODIUM THIOPENTAL (PENTOTHAL®), SODIUM METHITURAL (NERAVAL®), SODIUM BUTHALITONE (TRANSITHAL®), AND SODIUM HEXOBARBITAL (EVIPAL®)

GORDON M. WYANT, F.F.A.R.C.S., CHUNG AI CHANG, M.D., PH.D. (TOR.)
and EDWARD C. COCKINGS, M.B., CH.B.¹

MUCH HAS been written in recent years of the relative advantages and disadvantages of new intravenous anaesthetics. Such comparisons are always difficult to make because of the many variables which cannot be easily controlled in a clinical series. For that reason, we attempted some time ago to compare a number of intravenous agents in human volunteers, administering each drug consecutively to the same individuals under rigidly controlled conditions (1, 2). Double the sleep dose of each drug was given in a standard concentration and at a standard rate. For a variety of reasons the results obtained did not necessarily reflect each agent's usefulness in clinical practice. The standardization of concentration is a procedure open to criticism. Also, it is very difficult to determine equi-potent doses for each agent and the administration of double the sleep dose is not an exact criterion since the sleep dose itself is hard to define. It was felt that a further controlled study should be undertaken, restricting the administration of each agent to patients undergoing a standard operative procedure and using as the criterion of dosage the amount of drug required to permit the performance of the operation. The concentrations used in this study were the ones commonly employed in the clinical use of these agents.

It was hoped that the present clinical study would yield additional information which would enhance the value of our previous experimental results when considered side by side with them.

METHOD

As in previous clinical studies of intravenous anaesthetics (3, 4) the drugs were administered for minor gynaecological procedures only and their use was limited to patients in physical status 1 and 2. Freshly prepared 2½ per cent solutions of thiopental and methitural and 10 per cent solutions of buthalitone and hexobarbital were used. These concentrations are the ones used commonly in clinical practice. Anaesthesia was maintained by intermittent injection. The patients received oxygen by mask in a semi-closed system at a flow of 6 L per minute. Muscle relaxants were given only when muscle relaxation for pelvic examination was inadequate. All patients were premedicated with meperidine 50 mg. and atropine 0.4 mg intramuscularly. Fifty patients were studied in each series. Each drug was compared with thiopental and a further comparison was

¹From the Department of Anaesthesia, University of Saskatchewan College of Medicine and University Hospital, Saskatoon. Supplies of sodium methitural, sodium buthalitone, and sodium hexobarbital were made available through the courtesy of the Schering Corporation, Montreal, P.Q., Poulenc Ltd., Montreal, P.Q., and Winthrop Laboratories of Canada Ltd., Windsor, Ont., respectively.

made between methitural and buthalitone because these two agents are said to have some properties in common. Hence the methitural series is included in the present study although it has been published previously (3).

DISCUSSION OF RESULTS

Age, height, and weight (Tables I and II). Differences in the four comparisons were statistically not significant. Hence, the four groups are comparable as far as age, height, and weight are concerned.

TABLE I

AGE

	Oldest (yrs.)	Youngest (yrs.)	Mean (yrs) (mo)		S.D.
Thiopental	69	12	36	3	1 81
Methitural	72	16	34	9	0 90
Buthalitone	62	17	35	9	1 64
Hexobarbital	65	19	34	4	2 06

Comparisons: Thiopental/Methitural, $t = 0.677$, Thiopental/Buthalitone, $t = 0.230$, Thiopental/Hexobarbital, $t = 803$, Methitural/Buthalitone, $t = -0.442$.

S D = Standard Deviation.

TABLE II

HEIGHT AND WEIGHT

	Mean Height (in)	S D *	Mean weight (lb)	S D.
Thiopental	63 10	2 16	136 52	24 48
Methitural	63 10	2 31	129 69	23 64
Buthalitone	63 67	2 65	133 31	25 79
Hexobarbital	63 30	2 58	130 47	18 47

S D = Standard Deviation

Comparisons

Thiopental/Methitural	$t = 0$	$t = -1.211$
Thiopental/Buthalitone	$t = -1.180$	$t = 0.638$
Thiopental/Hexobarbital	$t = -379$	$t = 1.394$
Methitural/Buthalitone	$t = -1.145$	$t = -0.734$

Time from premedication to induction of anaesthesia (Table III). There was the usual wide variation in the time from premedication to induction. Only in the comparison of thiopental with methitural, is the difference of the mean

TABLE III

TIME FROM PREMEDICATION TO INDUCTION

	Longest (hr.) (min)		Shortest (min)	Mean (hr) (min)		S D.
Thiopental	2	49	2	1	20	28 94
Methitural	3	20	34	1	25	29.58
Buthalitone	3	27	0	1	38	32.05
Hexobarbital	2	41	40½	1	32	29 73

Comparisons: Thiopental/Methitural, $t = -0.806$; Thiopental/Buthalitone, $t = -2.908^{**}$; Thiopental/Hexobarbital, $t = -2.035^{*}$, Methitural/Buthalitone, $t = -2.117^{*}$.

S D = Standard Deviation

*Sig (Significant) ($P < .05$).

**H S (Highly Significant) ($P < .01$).

statistically not significant. Standardization of this variable has been found impossible under operating-room conditions.

Duration of anaesthesia and operation (Tables IV and V). Significant or almost significant differences were apparent in the thiopental-methitural and thiopental-buthalitone comparisons only. In the comparisons between thiopental and hexobarbital and between methitural and buthalitone, no such significant differences existed.

TABLE IV
DURATION OF ANAESTHESIA

	Longest (min)	Shortest (min)	Mean (min) (sec)		S.D
Thiopental	29	5	18	19	5.42
Methitural	28	4	15	2½	4.49
Buthalitone	33	7	16	14	5.31
Hexobarbital	33	9	19	23	6.15

Comparisons. Thiopental/Methitural, $t = 3.284^{**}$, Thiopental/Buthalitone, $t = 1.929^{\dagger}$, Thiopental/Hexobarbital, $t = -.931$, Methitural/Buthalitone, $t = -1.224$.

S.D. = Standard Deviation

** H.S. ($P < .01$)

† Almost, but not quite significant

TABLE V
DURATION OF OPERATION

	Longest (min)	Shortest (min)	Mean (min) (sec)		S.D
Thiopental	27	2	12	40	5.26
Methitural	23	4	9	41	4.26
Buthalitone	30	2	10	18	4.75
Hexobarbital	25	3½	11	46	5.35

Comparisons. Thiopental/Methitural, $t = 3.088^{**}$, Thiopental/Buthalitone, $t = 2.370^{*}$, Thiopental/Hexobarbital, $t = .840$, Methitural/Buthalitone, $t = -.0667$

S.D. = Standard Deviation

* Sig. ($P < .05$)

** H.S. ($P < .01$)

Total anaesthetic dose (Table VI) The differences in all four comparisons were statistically highly significant.

TABLE VI
TOTAL ANAESTHETIC DOSE

	Maximum (mg)	Minimum (mg)	Mean (mg)	S.D
Thiopental	1,000	250	585.5	146.39
Methitural	1,500	625	1,021	206.50
Buthalitone	2,100	800	1,498.4	352.78
Hexobarbital	3,000	900	1,528	471.34

Comparisons: Thiopental/Methitural, $t = -12.183^{**}$; Thiopental/Buthalitone, $t = -16.899^{**}$; Thiopental/Hexobarbital, $t = -13.503^{**}$; Methitural/Buthalitone, $t = -8.262^{**}$.

S.D. = Standard Deviation

** H.S. ($P < .01$).

Induction and maintenance doses (Tables VII and VIII). Significant differences existed in all four comparisons as far as the induction dose was concerned. The differences in the maintenance dose were statistically significant for the three comparisons with sodium thiopental, but the difference of the mean maintenance dose of buthalitone as compared with methitural was not significant.

TABLE VII
INDUCTION DOSE

	Maximum (mg)	Minimum (mg)	Mean (mg)	S D
Thiopental	250	75	244	30 12
Methitural	500	375	385	34 24
Buthalitone	1,000	450	521	86 95
Hexobarbital	700	500	522	54 55

Comparisons Thiopental/Methitural, $t = -21.933^{**}$, Thiopental/Buthalitone, $t = -21.291^{**}$, Thiopental/Hexobarbital, $t = -31.556^{**}$, Methitural/Buthalitone, $t = -10.287^{**}$

S D = Standard Deviation

** H.S. ($P < 01$)

TABLE VIII
MAINTENANCE DOSE

	Maximum (mg)	Minimum (mg)	Mean (mg)	S D
Thiopental	750	0	341.5	147.74
Methitural	1,125	250	636	206.84
Buthalitone	1,600	300	977	356.21
Hexobarbital	2,300	400	1,006	447.51

Comparisons Thiopental/Methitural, $t = -8.192^{**}$, Thiopental/Buthalitone, $t = -11.659^{**}$, Thiopental/Hexobarbital, $t = 9.977^{**}$, Methitural/Buthalitone, $t = -0.586$

S D = Standard Deviation

** H.S. ($P < 01$)

Dose per minute of anaesthesia (Table IX). Because of the significant difference in the mean duration of anaesthesia in the thiopental-methitural comparison and the almost significant difference in the thiopental-buthalitone

TABLE IX
DOSE PER MINUTE OF ANAESTHESIA

	Mean (mg.)	S D
Thiopental	34.91	15.14
Methitural	72.25	20.43
Buthalitone	98.06	27.89
Hexobarbital	84.92	33.62

Comparisons Thiopental / Methitural, $t = -10.384^{**}$, Thiopental/Buthalitone, $t = -14.065^{**}$, Thiopental/Hexobarbital, $t = -9.580^{**}$, Methitural/Buthalitone, $t = -5.278^{**}$.

S D = Standard Deviation.

** H.S. ($P < 01$)

comparison, the dose required per minute of anaesthesia was calculated. The differences in all four comparisons were highly significant. They indicated that thiopental was about twice as potent as any of the other three with methitural, hexobarbital, and buthalitone fairly close together in order of decreasing potency.

Total sleep time (Table X) This was defined as the time between induction of anaesthesia and the patient's purposeful response to verbal command. The differences in the thiopental-hexobarbital comparisons were statistically highly significant whereas the remaining three comparisons were not significant. This indicates that for a standard operative procedure there is no difference in the sleep time after thiopental, methitural, or buthalitone, whereas awakening following hexobarbital anaesthesia is greatly delayed.

TABLE X
TOTAL SLEEP TIME

	Longest (hr) (min)		Shortest (min)	Mean (min) (sec)		S,D
Thiopental	1	35	9	44	11	21 05
Methitural	1	10	23	40	12	12 24
Buthalitone	1	56	10	45	49	26 77
Hexobarbital	3	40	21	89	38	46 90

Comparisons Thiopental/Methitural, $t = 1.155$, Thiopental/Buthalitone, $t = -0.340$, Thiopental/Hexobarbital, $t = -6.252^{**}$, Methitural/Buthalitone, $t = -1.351$

S.D. = Standard Deviation.

** H.S. ($P < .01$).

Waking time from last injection (Table XI). This was the period from the last injection until the time when the patient responded to verbal command. Again, differences were statistically significant only in the thiopental-hexobarbital comparison and it is, therefore, concluded that hexobarbital has the longest action of the four agents studied. The other three agents have a very similar duration of action under the conditions of this study

TABLE XI
WAKING TIME FROM LAST INJECTION

	Longest (hr) (min)		Shortest (min)	Mean (min) (sec)		S D
Thiopental	1	25	7	31	49	18 90
Methitural	—	55	9	30	28	11 34
Buthalitone	1	39	5	33	16	25 20
Hexobarbital	3	32½	10	75		47 23

Comparisons Thiopental/Methitural, $t = -0.436$, Thiopental/Buthalitone, $t = -0.326$, Thiopental/Hexobarbital, $t = -5.997^{**}$, Methitural/Buthalitone, $t = -0.719$.

S.D. = Standard Deviation

** H.S. ($P < .01$).

Dose per minute of sleep time (Table XII). The differences in all four comparisons were statistically highly significant. Because of the prolonged sleep

after hexobarbital, the sequence here is thiopental, hexobarbital, methitural, buthalitone.

TABLE XII
DOSE PER MINUTE SLEEP TIME

	Mean (mg)	S D
Thiopental	15 57	9 72
Methitural	26 97	7 05
Buthalitone	42 74	20 82
Hexobarbital	20 54	9 58

Comparisons Thiopental / Methitural, $t = -6.709^{**}$; Thiopental/Buthalitone, $t = -8.360^{**}$, Thiopental/Hexobarbital, $t = -2.576^{**}$, Methitural/Buthalitone, $t = -5.071^{**}$

S D. = Standard Deviation

$^{**}H S (P < 0.01)$

Side effects (Table XIII). There was no significant difference between the incidence of *cough* in the thiopental-buthalitone and thiopental-hexobarbital comparisons. With methitural, the incidence during induction and maintenance was significantly higher than with either of the other three agents.

On the other hand the incidence of *hiccough* was greatest with buthalitone. There was no significant statistical difference between thiopental and methitural. With hexobarbital, *hiccough* was rare.

TABLE XIII
SIDE EFFECTS

	Cough incidence (%)	S D	Hiccough incidence (%)	S D	Movements incidence (%)	S.D
Thiopental	6	03	12	05	76	06
Methitural	22	06	24	06	86	05
Buthalitone	8	04	50	07	72	06
Hexobarbital	2	02	2	02	100	00

Comparisons

Thiopental/Methitural $t = -2.366^{**}$

$t = -1.581$

$t = -1.282$

Thiopental/Buthalitone $t = -0.392$

$t = -4.524^{**}$

$t = 0.455$

Thiopental/Hexobarbital $t = 1.026$

$t = 2.000^{*}$

$t = 4.000^{**}$

Methitural/Buthalitone $t = 2.000^{*}$

$t = -2.796^{**}$

$t = 1.750$

S D = Standard Deviation

$^{*}Sig (P < 0.05)$

$^{**}H S (P < 0.01)$

Movements occurred in many patients in all three groups. This was because slight movements were used as an indication for additional amounts of drug and may, therefore, be ignored for purposes of evaluation. Movements involving the legs to the point where such movements were noticed by the surgeon were

classified as moderate. Gross movements involved the entire body and included withdrawal of the pelvis. No such moderate or gross movements were seen under thiopental anaesthesia, but there was a significant incidence of these with both buthalitone and methitural, and they occurred in the majority of patients receiving hexobarbital (Table XIV). These severe movements could not always be adequately controlled by increasing the dose of the drug

TABLE XIV
MOVEMENTS

	None		Slight		Moderate		Severe	
Thiopental	12	(24%)	38	(76%)	0		0	
Methitural	7	(14%)	34	(68%)	5	(10%)	4	(8%)
Buthalitone	15	(30%)	29	(58%)	3	(6%)	3	(6%)
Hexobarbital	—	(0%)	13	(26%)	32	(64%)	5	(10%)

Apnoea (Table XV). The *incidence* of apnoea following an induction dose of thiopental was very high, significantly less so with methitural, even less so with buthalitone and least with hexobarbital. A similar relation applied to the mean *duration* of apnoea, this was longest with thiopental and shortest with hexobarbital.

TABLE XV
APNOEA

	Incidence	S D.	Longest (sec)	Shortest (sec)	Mean (sec)	S D
Thiopental	94% (47)	03	120	10	40.1	25.90
Methitural	58% (29)	07	70	1	21.2	23.62
Buthalitone	38% (19)	07	120	5	11.8	22.03
Hexobarbital	22% (11)	06	55	10	5.0	11.02

Comparisons

Thiopental/Methitural	$t = 4.622^{**}$	$t = 3.808^{**}$
Thiopental/Buthalitone	$t = 7.368^{**}$	$t = 5.884^{**}$
Thiopental/Hexobarbital	$t = 10.746^{**}$	$t = 8.841^{**}$
Methitural/Buthalitone	$t = 2.041^{*}$	$t = 2.061^{*}$

S D = Standard Deviation.

*Sig. ($P < 0.05$)

**H S. ($P < 0.01$)

Relaxants (Table XVI). Small doses of succinylcholine were given whenever muscular relaxation was inadequate for proper bimanual pelvic examination. From the analysis of the data, it would appear that both methitural and hexobarbital tend to relax slightly the lower abdominal muscles since relaxants were infrequently needed with these two drugs. The differences between them and thiopental were significant. The difference between thiopental and buthalitone was statistically not significant.

TABLE XVI

RELAXANTS

		S.D.
Thiopental	34% (17)	.07
Methitural	8% (4)	.04
Buthalitone	24% (12)	.06
Hexobarbital	4% (2)	.03

Comparisons: Thiopental/Methitural, $t = 3.377^{**}$, Thiopental/Buthalitone, $t = 1.562$, Thiopental/Hexobarbital, $t = 4.167^{**}$, Methitural/Buthalitone, $t = -3.137^{**}$.

S.D. = Standard Deviation

** H.S. ($P < .01$)

Emergence from anaesthesia (Table XVII). *Hiccough* was entirely absent after buthalitone, thiopental, and hexobarbital, but was relatively common after methitural. On the other hand, the incidence of *nausea and vomiting* was very high after hexobarbital. They occurred much less frequently following administration of the other three agents, with thiopental causing these reactions somewhat more frequently than the remaining two drugs.

TABLE XVII

EMERGENCE

	Depression and drowsiness	Restlessness	Emotional upset	Dizziness	Coughing	Hiccough	Vomiting and retching	Hypotension
Thiopental	1	—	—	1	—	—	5	—
Methitural	1	1	—	—	1	6	2	—
Buthalitone	—	—	—	—	—	—	3	—
Hexobarbital	—	1	1	—	—	—	21	1

Recovery period (Table XVIII). The incidence of post-anaesthetic *nausea and emesis* was relatively high after hexobarbital, lasting frequently as long as twelve hours. Three patients each experienced *vertigo and headache* following the drug. Two patients complained of headache following buthalitone and six others had vertigo. *Drowsiness and tiredness* were complained of by a small number of patients after thiopental, methitural, and buthalitone.

TABLE XVIII

RECOVERY PERIOD

	Irrational behaviour	Drowsiness and tiredness	Headache	Dizziness	Nausea and retching
Thiopental	—	1	—	2	—
Methitural	—	3	—	2	—
Buthalitone	—	2	2	6	—
Hexobarbital	1	—	3	3	7

SUMMARY

The claim that some of the newer barbiturates have a shorter duration than older agents has not been borne out by the present investigation in regard to thiopental, but is true in regard to sodium hexobarbital. If sodium thiopental, sodium buthalitone, or sodium methitural is used as the sole agent for a standard operative procedure, the least amount which will keep the patient quiet on the table being administered, there is no difference in the total sleep time or in the waking time from the last injection.

UNDESIRABLE SIDE-EFFECTS.

FIGURE 1. TH : Thiopental, M : Methitural, B : Buthalitone; H : Hexobarbital

If dose per minute of anaesthesia for such a standard procedure is taken as an indication, the relative *potency* of the four agents studied is: thiopental, 1; methitural, 0.5, hexobarbital, 0.4; and buthalitone, 0.35. The most potent agent shows the highest incidence of apnoea following induction and the longest mean duration of apnoea; the less potent ones have a lower incidence and a shorter mean duration of apnoea.

The incidence of *cough* during induction and maintenance is very much greater with methitural than with the other three drugs, whereas the incidence of hiccough during maintenance is much greater with buthalitone than with the

other three drugs. The incidence of moderate and gross *movements* following sodium hexobarbital is very high indeed. Sodium thiopental appears the most predictable and reliable of the four drugs, and it is invariably possible to control slight movements of patients and thus maintain smooth anaesthesia. With the other three drugs this is not always possible, and with sodium hexobarbital it is rarely possible, even when the amount of drug administered is markedly increased. Sodium methitural and sodium hexobarbital are the only ones which seem to *relax* abdominal muscles slightly. This action reduces the need for relaxants for bimanual pelvic examination considerably compared with the other two drugs.

In the post-anaesthetic period *hiccough* is again a relatively frequent phenomenon after methitural anaesthesia and *nausea and vomiting* are very common following hexobarbital. After buthalitone and hexobarbital *dizziness and headache* are more frequently seen than after the other two agents.

In summary, it appears that sufficiently large doses of the inherently shorter-acting methitural and buthalitone are required for smooth anaesthesia, so that total sleep time is in the end no different from thiopental. Anaesthesia is neither as smooth nor as predictable and free from annoying minor side effects as it is when thiopental is used. These disadvantages outweigh the shorter post-induction apnoea with methitural and buthalitone. The very high incidence of movements during anaesthesia, the long postoperative sleep and the high incidence of nausea and emesis in the post-anaesthetic period far outweigh the low incidence and duration of post-induction apnoea following sodium hexobarbital anaesthesia.

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RÉSUMÉ

Nous avons administré, en doses fractionnées, à cinquante femmes en santé qui devaient subir des opérations gynécologiques mineures, du thiopental de sodium (Pentothal®), du methitural de sodium (Neraval®) du buthalitone de sodium (Transithal®) et de l'hexobarbital de sodium (Evipal®). Nous avons comparé le methitural de sodium, le buthalitone de sodium et l'hexobarbital de sodium avec le thiopental de sodium et le methitural de sodium avec le buthalitone de sodium. Nous avons employé des solutions à 2½% pour le thiopental et le methitural et des solutions à 10% pour le buthalitone et l'hexobarbital. Nous avons observé que, pour une opération ordinaire régulière, si nous employons, comme seul agent, le thiopental, le buthalitone ou le methitural, la durée totale du sommeil pour chacun des agents était la même. Après l'emploi de l'hexobarbital, la durée du sommeil est beaucoup plus longue. Le pouvoir relatif des trois agents est: le thiopental, 1, le methitural, 0.5; l'hexobarbital, 0.4;

et le buthalitone, 0.35. En ce qui concerne l'apparition et la durée d'apnée, le thiopental se classe premier et l'hexobarbital dernier. Le plus fiable des quatre agents étudiés a été le thiopental; nous l'avons réussi avec lui à maintenir une douce anesthésie, ce que nous ne pouvons pas dire des trois autres. Nous avons noté de la toux plus souvent avec le methitural qu'avec les deux autres agents, du hoquet plus souvent avec le buthalitone et des mouvements de toute amplitude durant l'anesthésie à l'hexobarbital. Nous avons observé un léger effet myoré-solutif sur les muscles de l'abdomen inférieur avec le methitural et l'hexobarbital de sodium et non pas avec le thiopental et le buthalitone. Après l'anesthésie, le hoquet est relativement plus fréquent avec le methitural et, après l'hexobarbital, il y a plus de nausées et de vomissements. Après le buthalitone et l'hexobarbital, nous avons observé très souvent de la céphalée et des étourdissements.

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