PROPANIDID—A NEW NON-BARBITURATE INTRAVENOUS ANAESTHETIC

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THE SEARCH continues for new and improved hypnotics, free, as much as possible, from the disadvantages of barbiturates used over prolonged periods. It is logical then that this search should have been extended to the field of intravenous anaesthetics. Here, for all intents and purposes, the barbiturates at present hold a monopoly. Although intravenously administered so-called ultra short-acting barbiturates do not have the same disadvantages as other barbiturates used over long periods, nevertheless there are sufficient drawbacks to them to warrant the search for other agents. One need only think of the powerful central depression of respiration which these drugs exert, their hypotensive potential, their parasympathomimetic effects, their instability in solution, the complications associated with their strong alkalinity, to mention only a few problems, to appreciate that these agents, indispensible as they are at present, by no means satisfy our concept of an ideal anaesthetic. Another disadvantage frequently attributed to the ultra short-acting barbiturates is the prolonged recovery from the anaesthetic and the persistence of hang-over. While this disadvantage undoubtedly occurs with the majority of these drugs, it is not a characteristic of the group as such, as it has been shown that awakening from methohexital is very prompt indeed.

Because of what has been said, the advent of a non-barbiturate intravenous anaesthetic, far enough advanced to reach the stage of clinical testing, is always an interesting development, and any such agent deserves thorough evaluation.

BACKGROUND

One group of non-barbiturate intravenous anaesthetics comprises those which are derivatives of eugenol, the active principle in clove oil. This substance is used extensively in dental practice primarily for its sedative effect on dentin. The agents in this group are all derivatives of phenyloxyacetic acid, and the three agents which have reached the stage of clinical trial out of a large number of substances synthesized are G29505 (Eunal), E34 (Propinal) and FBA 1420 (Propanidid). The chemical similarity of these substances becomes evident from perusal of their chemical formulae (Fig. 1).

G29505

Swerdlow in 1961 published one of the earliest papers in the English literature on G29505,[1] followed in 1962 by Dundee and Rajagopalan,[2] and in the following year by Stephen and Rippy.[3] All these authors agree that injection of this drug

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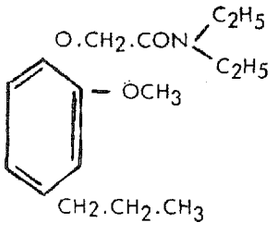
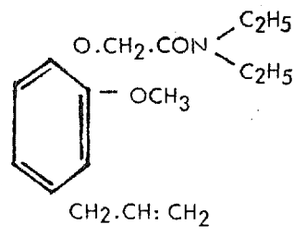
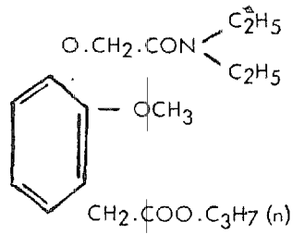


2-M-4-P
PROPINAL



2-M-4-A
G 29505 - EUNAL



BAYER 1420
PROPANIDID

FIGURE 1

is followed by a period of vigorous hyperventilation followed by hypoventilation or even apnoea, and that hyperventilation can again be produced by subsequent injection. There is further consensus that damage to veins occurs in a significant number of instances, that involuntary muscle movements are observed, that the incidence of postoperative nausea and emesis is higher than with the commonly used intravenous barbiturates, and that there is relatively little interference with circulatory parameters. In addition, Stephen noted the occurrence of haemolysis following injection of the drug. Riding, Dundee, Rajagopalan, Hamilton, and Baskett,[4] while confirming some of the afore-mentioned complications, have noted that muscle movements, cough, hiccough, and laryngospasm were much more frequent when hyoscine was used for premedication instead of either atropine or a narcotic with atropine.

Be this as it may, the prediction of Boureau[5] of a great future for this drug has not been fulfilled, and apart from scattered references in the literature, it is today of historic interest only.

Propinal

Meanwhile in 1962, Nishimura[6] had published a paper on Propinal, the second drug in this series. He found it to be a useful adjuvant to nitrous oxide anaesthesia or to regional block, and he noted that after initial stimulation, respiration became moderately depressed. He found no adverse effects on the cardiovascular system and noted a minimum of post-operative complications. However, he observed that if atropine was omitted from the premedication, nausea, vomiting,

and coughing would easily occur, and that lymphangitis had been noted in some of his patients. Propinal also failed to prove itself and has now been abandoned.

Chemistry of Propanidid and Review of Literature

Propanidid (FBA 1420) is the latest member of the family of eugenol derivatives to be introduced for clinical trial. Its chemical name is 3-methoxy-4-(N,N diethyl carbamidomethoxy) phenylacetic acid-n-propylester. It is a faintly yellow, oily substance, insoluble in water. An emulsifier is used to put the active principle into an aqueous solution containing 0.9 per cent sodium chloride. The substance may be diluted with water or normal saline, and the active principle does not precipitate.

Several papers in the English literature began appearing in May, 1964. Radnay,[7] in a series of 150 short surgical procedures, found that there was an initial central stimulation to respiration followed by respiratory depression. He emphasized the lack of side-effects or local irritation and the speed with which patients were able to return to their duties following recovery from the anaesthetic. He thought the drug was suitable as the exclusive anaesthetic for short surgical procedures or as a supplement to regional anaesthesia, and he suggested a dose of 10 mg./kg., with a minimum of 350 mg. and a maximum of 750 mg. for a single injection at a rate of 1 ml. per second. He suggested that injection into an intravenous drip rather than directly into a vein would avoid local irritation.

Almost simultaneously, Howells, Odell, Hawkins, and Steane[8] concluded that Propanidid might have a useful place in anaesthesia, but made two reservations. One was based on the unpredictable degree of post-hyperpneal depression following doses in excess of 5 mg./kg.; the other had to do with the unpredictability of the duration of apnoea when the drug was used in conjunction with a short-acting depolarizing muscle relaxant. The found a low incidence of thrombophlebitis, and they emphasized the short action and rapid recovery. They implied, however, that this very short action may have inherent disadvantages in in-patient anaesthesia. Furthermore, they were not impressed by the analgesic properties of Propanidid, and suggested that it be supplemented by nitrous oxide–oxygen.

Dundee and Clarke[9] felt that the transient nature of the analgesia produced was not likely to make the drug's clinical application a significant factor. As part of a series of clinical studies of induction agents and specifically their influence on the respiratory effects and sequelae of suxamethonium, the same authors, in co-operation with Daw,[10] came to a conclusion similar to that of Howells and his co-workers,[8] namely that the phenyloxyacetic acid amines such as Propanidid and G29505 seem to exert a potentiating influence on suxamethonium.

Goldman and Kennedy[11] compared the advantages with the disadvantages of Propanidid on the basis of 230 unselected short dental anaesthetics. They list as advantages the fast recovery from the drug and ability of the patients to leave after out-patient procedures, and in this connection they stressed smooth recovery with absence of hang-over. They found that hyperventilation following induction facilitated blind nasal intubation and they noted a very low incidence of drop of

blood pressure. They noted further that the agent had analgesic properties. As disadvantages they cited the viscosity of the solution, which necessitated a large-bore needle for injection, as well as a high incidence of haematomata and one case of venous thrombosis. In the presence of halothane there was an increased incidence of hypotension and they felt that the incidence of postoperative nausea and vomiting was increased.

Lastly, Harnik[12] studied the biphasic ventilatory effects of Propanidid which has been noted by other authors, and found that the effects of Propanidid on ventilation depended largely upon dosage. In the lower dose range of 5 mg./kg., respiratory stimulation was not marked and depression was moderate with only occasional apnoea, whereas with the higher dose of 10 mg./kg., both stimulation and the ensuing depression were marked.

Present Study

On the basis of the information so far available, it seemed that this agent warranted further clinical study, and it was therefore decided to carry out such an investigation. The study, while a clinical one, was to be sufficiently controlled to allow at least some conclusions to be drawn from it. Essentially, the drug was to be studied under two conditions, namely (1) as an induction agent and as supplement to nitrous oxide-oxygen maintenance in women undergoing dilatation and curettage, and (2) as the sole anaesthetic agent for electroshock therapy with succinylcholine modification of the convulsions.

Clinical Anaesthesia

Fifty patients undergoing E.U.A. and D. & C., with or without biopsy of cervix, were studied. All patients were premedicated with meperidine 50 mg. and atropine 0.6 mg. intramuscularly as closely within one hour of induction of anaesthesia as possible. Induction was with 2½ per cent Propanidid injected into an intravenous infusion of normal saline previously set up with a 15-gauge Rochester needle. This was followed by nitrous oxide-oxygen, 8 and 2 litres per minute respectively, and supplemented by Propanidid whenever required. Emergency procedures or patients who had severe systemic disease were excluded from the study.

Originally in this series the induction dose was calculated on the basis of 10 mg./kg. However, that dosage was abandoned since postoperative nausea, vomiting, and headaches were severe and prolonged, extending at times over a day or two. The study was started again and this time was conducted on fifty patients who received in induction dose of 5 mg./kg.

In the ultimate analysis, a new agent must bear comparison with established drugs used for similar purposes, and therefore it was initially thought desirable to conduct a blind comparative study with thiopental. Unfortunately it was impossible to mask the two drugs in such a way as to prevent recognition by physical properties. Propanidid, it will be recalled, is an oily substance, and the addition of a colouring agent to both it and thiopental failed to produce the same colour in both drugs. Thus the attempt at a blind study had to be abandoned.

However, three patients who had received Propanidid were subsequently anaesthetized for another D. & C. with thiopental, and these cases are available for comparison. Also, since similar series under identical conditions have been conducted in the past for thiopental and methohexital[13] in our department, it was decided to use these data as a basis of comparison with Propanidid.

Electroshock Therapy

The second part of the study was concerned with the evaluation of Propanidid as compared with thiopental in fifty patients undergoing electroshock therapy. In all cases the intravenous anaesthetic was supplemented by succinylcholine to modify the convulsive reaction. Since all patients had more than one treatment, each patient could serve as his own control, and thiopental and Propanidid were administered in random sequence. Fifty consecutive patients were studied who had had two or more treatments. Altogether these fifty patients had 126 treatments under thiopental anaesthesia and 171 under Propanidid; injection was direct into the vein.

All treatments were handled in identical fashion. On arrival in the treatment room, atropine 1 mg. was administered intravenously, followed immediately by either Propanidid or thiopental, and that in turn by intravenous succinylcholine 15 mg. After fasciculations had disappeared, the electroshock was administered. Care was taken that at least one minute had elapsed between the administration of atropine and the application of the electric current. As soon as that had been completed, the patient's lungs were ventilated with oxygen until adequate spontaneous respiration was re-established. Thereafter the patients were moved to the adjoining observation room.

Results

Clinical Anaesthesia

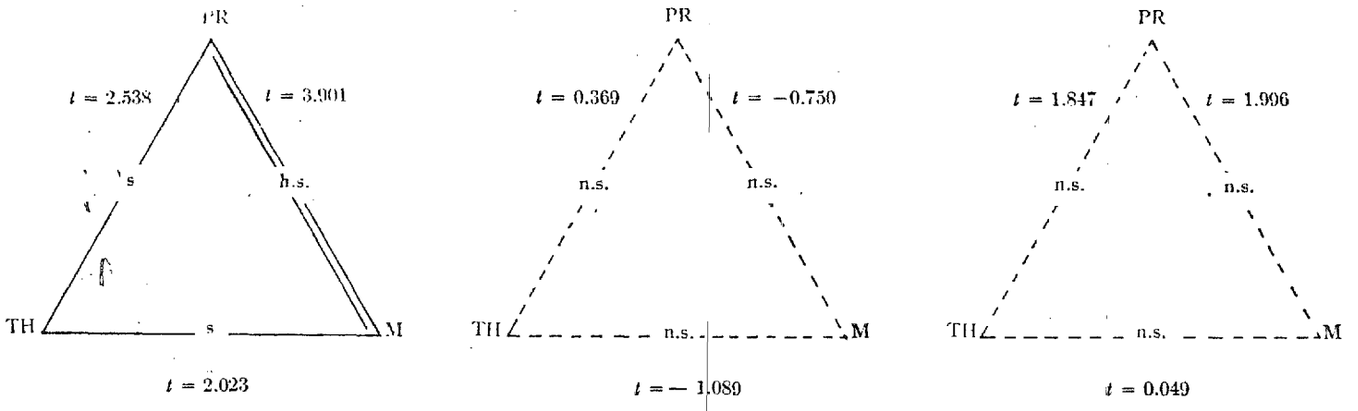
Basic Patient Data (Table I). The mean age, height, and weight for the fifty patients in this study are given, as well as the data published previously for thiopental and methohexital, added here for purposes of comparison. While the average age of the patients in the thiopental series is significantly lower than that of patients in the Propanidid series, and the age of the methohexital patients is lower still, there is no significant difference among the groups as far as height and weight are concerned. There is a slight increase in the average weight of the Propanidid patients which can well be explained on the basis of the greater age of this group, but it is not statistically significant. The age difference in the three series does place some limitations on the value of comparisons of other parameters, but if such differences are marked, one is still permitted to draw conclusions within certain limits from the findings.

Duration of anaesthesia and operation (Table II). While the mean duration of operation for all three series was identical, the mean duration of anaesthesia, that is, the time from induction of anaesthesia until nitrous oxide-oxygen inhalation was discontinued, was significantly longer for the Propanidid series than for

TABLE I
BASIC PATIENT DATA

	Mean age years	months	s.d.	Mean height cm.	s.d.	Mean weight lb.	s.d.
Propanidid	40	2	10.97	63.67	2.23	139.96	24.24
Thiopental	35	7	7.09	63.5	2.5	130.8	26.8
Methohexital	31	11	10.66	64	2.3	130.5	24.3

Comparison:



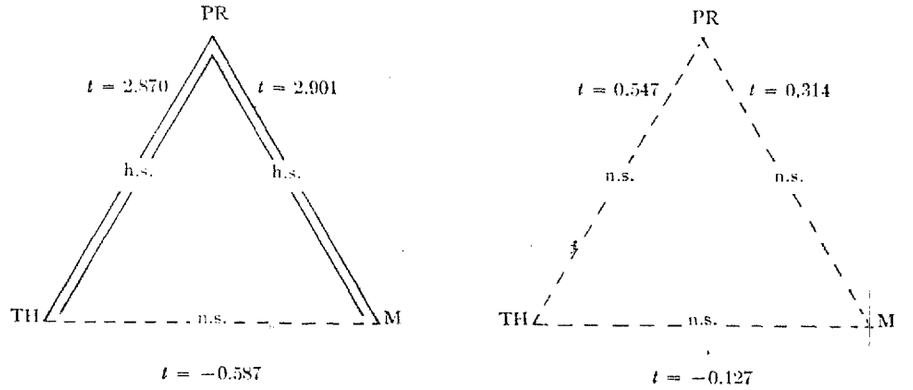
PR = Propanidid
TH = Thiopental
M = Methohexital
n.s. = Statistical non-significance, indicated by a broken line
s. = Statistical significance ($p < .05$), indicated by a single line
h.s. = Statistical high significance ($p < .01$), indicated by a double line

either thiopental or methohexital. As will be seen later, this was due to the fact that several anaesthetics were so stormy that the start of operation had to be delayed until the patient could be brought adequately under control.

TABLE II
MEAN DURATION

	Anaesthesia minutes	s.d.	Operation minutes	s.d.
Propanidid	21.36	7.47	12.68	5.80
Thiopental	17.6	5.8	12.1	5.0
Methohexital	18.4	7.3	12.3	6.6

Comparison:



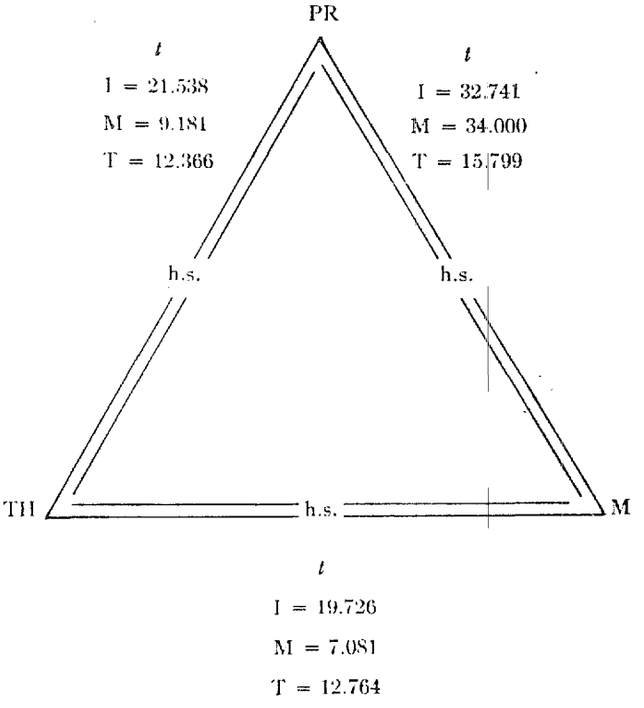
Abbreviations as in Table I.

Mean amount of drug used (Table III). Not too much significance should be attributed to the figures recorded here. Since Propanidid is not a barbiturate, any comparison with the other two barbiturate drugs in terms of quantity could be quite misleading. It might be noted, however, that for Propanidid the mean dose was 1 gm. divided in the ratio of 1:2 for induction and maintenance, these ratios being much smaller for the other two agents.

TABLE III
MEAN AMOUNT OF DRUG USED

	Induction		Maintenance		Total	
	mg.	s.d.	mg.	s.d.	mg.	s.d.
Propanidid	318.1	55.35	682.5	390.9	1000.6	393.21
Thiopental	133.3	26.3	161.8	94.8	295.1	95.3
Methohexital	54.2	14.2	65.4	37.2	119.6	38.4

Comparison:



Abbreviations as in Table I.

Recovery period (Table IV). Four different figures are available. The mean sleep-time is defined as the time elapsing from induction by means of the intravenous injection of the agent under study until the patient obeys the simple verbal command to open the eyes. The mean waking time has been recorded both from the last injection and from the end of inhalation anaesthesia, and again its end-point is the obedience to a simple verbal command. The last parameter recorded is the mean time from wake-up, that is, obedience of a simple command, to full orientation as to place and time.

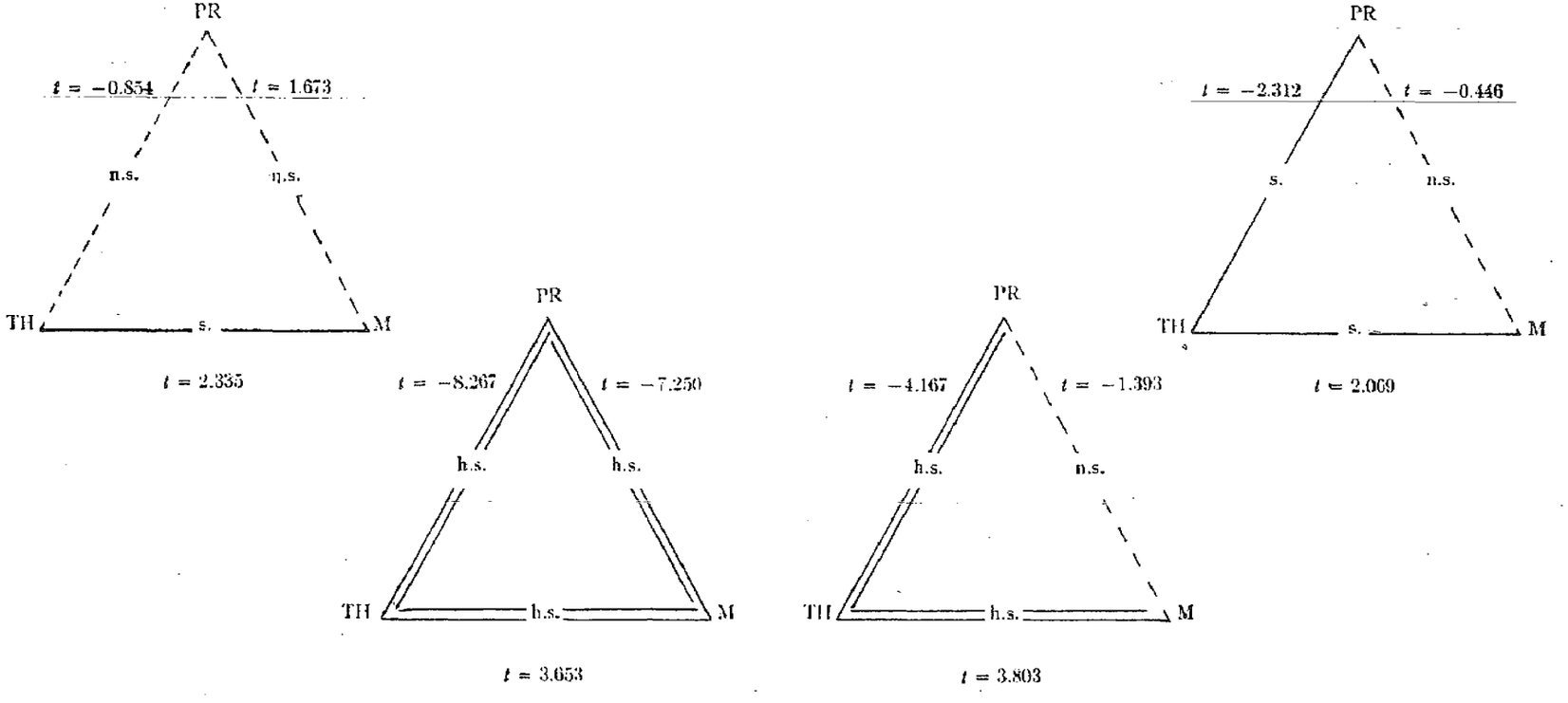
As far as the sleep-time is concerned, Propanidid falls half-way between thiopental and methohexital, but none of the differences is significant. The waking time elapsing after the last injection is very significantly shorter with Propanidid than with either of the other two agents. The waking time after the end of the inhalation anaesthesia, on the other hand, is essentially identical to that with

TABLE IV

RECOVERY

	Mean sleep time		Mean waking time: (a) from last injection		Mean waking time: (b) from end of inhalation anaesthesia		Mean wake-up to orientation		
	min.	s.d.	min.	s.d.	min.	s.d.	min.	sec.	s.d.
Propanidid	23.71	8.23	4.5	1.46	2.235	1.528	1	19	84.7
Thiopental	25.3	10.9	15	9.4	7.7	9.7	2	14	151.6
Methohexital	21.1	7.7	10.3	5.7	2.7	1.8	1	26	85.1

Comparison:



Abbreviations as in Table I.

methohexital, but very significantly shorter than with thiopental. One must come to the conclusion that in order to maintain anaesthesia, injection of Propanidid has to be carried further along towards the end of the operation than was necessary with methohexital. The data indicate that Propanidid is even shorter-acting than methohexital. The identical waking time from end of inhalation anaesthesia for these two drugs indicates that in both instances the effect of the intravenous agent had for all intents and purposes worn off and patients awoke largely as from nitrous oxide anaesthesia. In the case of thiopental, sufficient drug effect was still present to delay wakening time quite markedly. Orientation occurred equally speedily after Propanidid and methohexital, and almost twice as fast as after thiopental.

Side-effects (Table V). There were many side-effects in the course of anaesthesia with Propanidid, and some of them made the conduct of anaesthesia most difficult and unsatisfactory. Some of the phenomena, such as breath-holding, moving, phonation, emesis, and swallowing may be largely explained by the fact that anaesthesia was kept light, and a minimum of the intravenous anaesthetic was used. On the other hand, when these phenomena became very severe and could not be controlled by any amount of additional drug, as happened in nine instances, then the anaesthetic had to be listed as thoroughly unsatisfactory. The eighteen separate instances of rigidity encountered could normally have been controlled by the administration of a muscle relaxant. This was not done in our series, in order to observe more closely all effects of the drug itself. However, succinylcholine was needed on three occasions when it was completely

TABLE V

SIDE-EFFECTS

Rigidity	18	
(a) difficult to put legs into stirrups		11
(b) abdominal, hindering pelvic examination with or without (a)		5
(c) impossible to insert airway but no (a) or (b)		1
(d) difficult to insert airway but no (a) or (b)		1
Shivering	1	
Coughing and bucking on airway	5	
Hiccough	1	
Breath-holding	5	
Moving	24	
controlled by additional drug		17
not controlled by additional drug		7
Phonating	24	
controlled by additional drug		22
not controlled by additional drug		2
Swallowing	14	
Emesis during operation	2	
Unpleasant taste on induction	1	
Cardiovascular*		
hypotension—induction		3
—maintenance		1
hypertension—induction		2
—maintenance		1

*Changes exceeding 20%.

impossible to control the patients on the table before the operative procedure could be carried out. Coughing and bucking on the airway was noticeable and disturbing in five cases. One patient stated that she "heard voices" throughout the procedure, but did not feel any discomfort. This had been a very unsatisfactory anaesthetic because of uncontrollable movement, despite a total of 1175 mg. of Propanidid, and there had been hiccough, rigidity, phonation, and swallowing. On the other hand, the incidence of hypotension in excess of 20 per cent of the original systolic blood pressure compares favourably with that under other intravenous anaesthetics, and indeed hypertension occurred in three instances. Hyperventilation in varying degrees always occurred, but in all instances this phenomenon was followed by a brief period of apnoea only if hyperventilation had been vigorous.

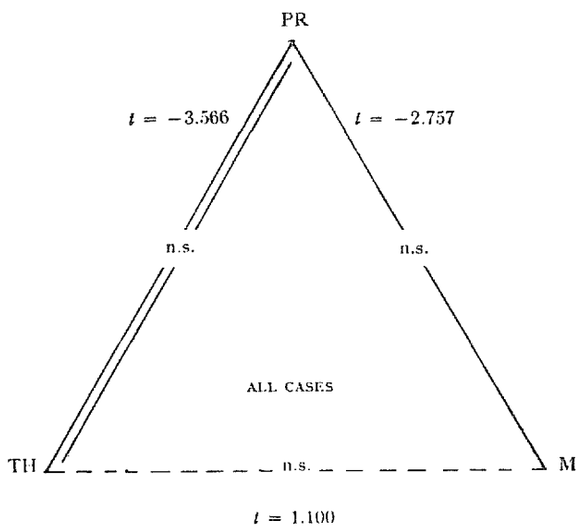
The question must be asked whether the smoothness or roughness of the anaesthesia was influenced in any way by the *preoperative medication* (Table VI). There is a highly significant difference when the Propanidid series is compared with the thiopental series and a significant difference when it is compared with the methohexital series. On the whole, premedication in the Propanidid series was administered closer to the time of induction. Therefore it can perhaps be assumed to have influenced the course of anaesthesia differently than in the other two series. When the mean time from premedication to induction of anaesthesia of all fifty Propanidid cases is compared with the twenty-two satisfactory anaesthetics on the one hand, and the twenty-eight unsatisfactory anaesthetics

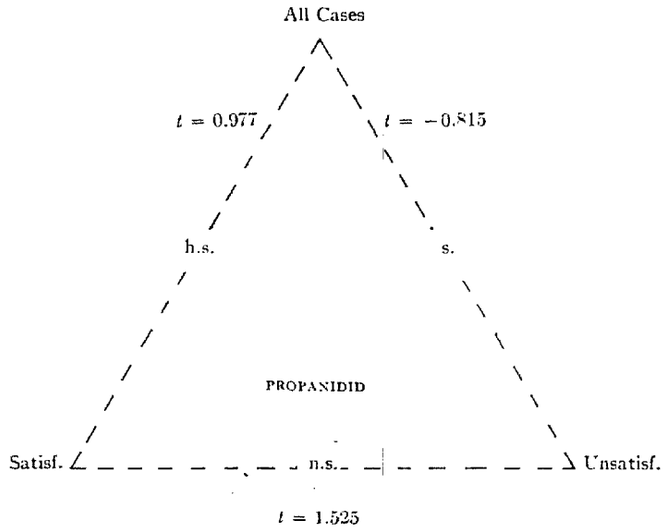
TABLE VI

MEAN TIME FROM PREMEDICATION TO INDUCTION

	All cases			22 satisfactory anaesthetics			28 unsatisfactory anaesthetics		
	hr.	min.	s.d.	hr.	min.	s.d.	hr.	min.	s.d.
Propanidid	1	13.8	31.578	1	6	30.651	1	19	31.496
Thiopental	1	39	40.9						
Methohexital	1	31	32.24						

Comparison:





Abbreviations as in Table I.

on the other, and when satisfactory and unsatisfactory anaesthetics are compared with each other, no difference can be demonstrated. It is therefore concluded that the time of administration of the preoperative medication did not determine whether an anaesthetic with Propanidid was going to proceed smoothly or otherwise.

It was noted, however, that insertion of an oral air-way was, on the whole, poorly tolerated, and that anaesthesia could be conducted smoothly in many more cases if an airway was omitted. Indeed, of the twenty-two smooth anaesthetics, fifteen patients (68%) had no oral airway, whereas in the twenty-eight unsatisfactory anaesthetics, eighteen patients (62%) did have an oral airway inserted. This certainly does not explain all the unsatisfactory anaesthetics, but seems to have been a factor in them.

Postoperative period (Table VII). It will be seen that nausea and emesis, or emesis alone, occurred in a total of twenty-nine instances, much more frequently than with either thiopental or methohexital. The same observation applies to postoperative headaches.

Three patients complained of an unpleasant taste postoperatively, but one volunteered that she felt better than after a previous D. & C.

TABLE VII

POSTOPERATIVE PERIOD

	Nausea and emesis	Nausea only	Emesis only	Headache
Propanidid	16	11	2	5
Thiopental	5	1	—	1
Methohexital	1	1	—	0

Direct comparison. While this study was in progress, three patients underwent D. & C. twice. Of these, one had received Propanidid in the dose of 10 mg./kg. for induction early in the investigation and before this dosage had been abandoned. This was one of the instances in which the case proceeded smoothly with 10 mg./kg., and therefore it is of interest to mention it here. The other two patients were among the main series of fifty patients who received an induction dose of 5 mg./kg. All were given thiopental on the second occasion (Table VIII).

The comparisons in all three cases suffer from failure to administer the premedications at comparable intervals before the induction of anaesthesia. Nevertheless postoperative wakening and orientation were always markedly prolonged for thiopental as compared with Propanidid, quite out of proportion to the difference in premedication time. One must also bear in mind that the relation of premedication to induction was different in each case and even reversed in the second case. Cardiovascular changes were not obvious and the one case of hypertension on induction may well be attributed to the rather large dose of 10 mg./kg. Only in the 10 mg. case was anaesthesia smooth with Propanidid. In the second one, anaesthesia was so difficult that succinylcholine had to be given to settle the patient and allow the operation to proceed. In the third case, continuous movement and tightness were quite disturbing. Anaesthesia with thio-

TABLE VIII

	I		II		III	
	Propanidid, 10 mg./kg.	Thiopental	Propanidid, 5 mg./kg.	Thiopental	Propanidid, 5 mg./kg.	Thiopental
Age (years)	15	15	21	21	35	35
Duration of anaesthesia (min.)	15	14	35	17	35	35
Duration of operation (min.)	10	7	14	8	22	25
Hypertension	ind.	—	—	—	—	—
Amount used for induction (mg.)	590	150	315	315	300	300
Amount used for maintenance (mg.)	50	150	1575	200	700	500
Total amount used (mg.)	440	300	1890	515	1000	800
Time from premedication to induction (min.)	105	82	88	115	103	30
Waking time (min.)	1.5	8	4	20	1.25	13.5
Orientation (min.)	2	19.5	6	21	1.25	very drowsy
Nausea and emesis	yes	no	yes	no	yes	no
Headache	no	no	no	no	yes	no
Remarks	smooth	smooth	succinylcholine to control	smooth	movement and tightness	smooth

pental was smooth in all instances. All three patients had nausea and emesis in the immediate postoperative period after Propanidid, a phenomenon which was absent with thiopental. In addition, the third patient had severe postoperative headache, and this again did not occur after thiopental. However, she was very drowsy for a long time after thiopental, well beyond the period of reaction to verbal command, but this may well have been occasioned by the late intramuscular administration of the premedication which no doubt did not exert its influence until after the operation had been completed.

Electroshock Therapy

The vital statistics of these patients, the number of treatments with each agent, and the dose ranges for each are listed in Table IX.

The mean dose and the waking time after each drug are listed in Table X. As in the D. & C. study, there is a difference in the mean dose administered, a very significantly larger amount of Propanidid being required. It is stressed again that this is of academic interest only and does not add to or detract from the merits of either agent. The mean waking time was considerably longer for Propanidid in the electroshock cases than it was in the D. & C. study. This is almost certainly due in part to the effects of the electric current and in part to the lesser reliability in determining the endpoint in patients with psychiatric disorders. Nevertheless, the comparison with thiopental is valid, since each patient served as his own control and therefore the same conditions prevailed for both drugs. In some few instances the exact wakening time could not be determined at all, and in those cases the data are omitted from the statistical analysis. Results of the analysis show that patients after Propanidid awoke significantly earlier than after thiopental.

There were no major troublesome side-effects from either thiopental or Propanidid in this entire series, nor was nausea or emesis observed. The only exception was one patient who had nausea and emesis after the first three treatments, one of them conducted under thiopental and two under Propanidid. The patient was then given dimenhydrinate before each shock treatment during the next three treatments, all of which were done under thiopental, and no postoperative nausea and emesis developed. However, the next three treatments under Propanidid, with dimenhydrinate omitted from the preparation, still did not result in nausea and emesis. One might safely assume therefore that the occurence of this sequel after the first three administrations was likely related to factors other than the anaesthesic agents.

No thrombophlebitis was noted, despite the fact that injections were made directly into the veins. Neither was apnoea following the injection of succinylcholine more prolonged when Propanidid rather than thiopental was used as the anaesthetic. However, it was noted that after Propanidid, patients had some residual weakness as manifested by the difficulty of opening their eyes, raising their arms, etc. This was likely a residual effect of the muscle relaxant, but it is difficult to be certain whether it can be interpreted as potentiation or whether it was simply due to the fact that patients awoke more rapidly after Propanidid before full muscle power could return.

TABLE IX

LIST OF ELECTROSHOCK THERAPY PATIENTS

Patient no.	Age	Height (in.)	Weight (lb.)	Diagnosis	Dosage range		No. of treatments	
					Thiopental (mg.)	Propanidid (mg.)	Thiopental	Propanidid
1.	52	64¼	121	involutional melancholia	75	75–200	1	5
2.	52	67½	155	involutional melancholia	75	100–200	1	4
3.	23	64	116	puerpural psychosis	75	75–125	2	3
4.	57	66	125	acute anxiety	100	75–150	2	3
5.	57	61½	144	involutional depression	75–150	75–200	6	6
6.	21	67¼	168	manic depressive psychosis	75–100	75–200	4	5
7.	45	67½	205	reactive depression	100–150	100–200	2	7
8.	50	61½	92	paranoid schizophrenic	75–100	100–200	2	5
9.	46	68¼	147	schizophrenic	100–150	100–200	3	5
10.	55	64¼	136	involutional depression	75–150	150–200	4	4
11.	67	60½	95	paranoid schizophrenia	100	75–150	1	4
12.	53	65	140	schizophrenia	75–200	100–250	6	7
13.	45	72¼	167	paranoid schizophrenia	100–150	75–200	3	6
14.	28	67	161	puerperal depression	75	150	2	1
15.	27	66½	127	depression	75–150	100–200	2	3
16.	35	62	131	schizophrenia	75–100	75–200	3	4
17.	57	60½	115	schizophrenia	75–125	100–150	3	5
18.	40	66½	138	depression	75–125	75–150	3	3
19.	36	68½	158	neurasthenia—reactive	125	100–200	2	4
20.	38	66½	145	depression (manic)	75	150	1	1
21.	67	57½	119	chronic anxiety state	75–100	100–150	2	3
22.	71	68	200	depression	125	150–250	1	3
23.	49	68½	155	psychotic depression	100–150	100–200	4	5
24.	60	61	110	depression	100–150	100–150	2	7
25.	45	65¼	145	schizophrenia	125–150	100–200	2	4

TABLE IX *(Concluded)*

Patient no.	Age	Height (in.)	Weight (lb.)	Diagnosis	Dosage range		No. of treatments	
					Thiopental (mg.)	Propanidid (mg.)	Thiopental	Propanidid
26.	41	61½	124	depression	100–125	100–125	2	4
27.	24	67	130	post-partum depression	100–125	100–150	3	3
28.	53	60½	173	schizophrenia	100	100–150	1	3
29.	62	57½	165	manic depression	150	150–200	1	3
30.	38	63	141	manic depression	100	150–200	1	2
31.	33	69¼	122	N.Y.D.	150	150	1	1
32.	56	61½	143	involutional depression	100–150	100–200	3	3
33.	41	65½	150	manic depression	100	100–150	1	3
34.	47			depression	125	125	1	1
35.	43	63½	121	depression	125	125	1	1
36.	49	73	204	paranoid schizophrenia with depression	100–200	150–200	4	3
37.	61	64¼	198	depression	125–200	150–200	3	3
38.	63	58½	151	depression	125	125	1	1
39.	54	66½	150	depression (psychotic)	75–200	100–200	5	4
40.	42	70	158	depression	75–125	100–125	2	2
41.	23	62	118	schizophrenic	75–125	75–175	2	3
~~42.~~	~~40~~	~~68½~~	~~146~~	~~depression~~	~~100~~	~~75–100~~	~~1~~	~~2~~
43.	72	65½	138	paranoid schizophrenic	75–150	100–150	7	5
44.	53	64¼	108	depression	75–125	75–125	3	3
45.	40	65¼	214	schizophrenia	150	150	4	4
46.	43	65½	165	schizophrenia	100	100	2	2
47.	19	67¼	151	depression (manic)	75–100	100	3	2
48.	74	58½	98	depression	100	100	1	1
49.	50	63	118	depression	75–100	75–150	4	4
50.	45	63	157	N.Y.D.	75–125	75–125	5	3

TABLE X
ELECTROSHOCK THERAPY

	Mean dose			Mean waking time		
	mg.	s.d.	t	min.	s.d.	t
Propanidid	136.783	41.43	5.846*	5.74	2.76	4.844*
Thiopental	112.46	32.25		7.92	4.38	

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

SUMMARY AND CONCLUSION

Experience gained from the use of Propanidid in fifty D. & C.'s would indicate that the drug is a rapid-acting induction agent. When it is also used to supplement nitrous oxide anaesthesia, undesirable side-effects such as rigidity, coughing, hiccough, phonation, and uncontrollable movement of the patient occur in a sufficiently large percentage of cases to make this an undesirable anaesthetic technique. There is no evidence that the side-effects are influenced by the timing of the premedication, but it would appear that if no oral airway is inserted, the percentage of smooth anaesthetics can be increased. While this possibility was not further explored, it would seem that many of the undesirable manifestations in this series could have been controlled by the addition to nitrous oxide of a more potent inhalation anaesthetic and/or the administration of a short-acting muscle relaxant. In the latter case however, the supplemental doses of Propanidid would not have been required in the first place, except perhaps early during maintenance to allow a smooth transition from induction. It is feared that the short effect of a single induction dose of Propanidid might have made such transition difficult. Our comparisons indicate that if rapid awakening from a short anaesthetic is desirable and anaesthesia is to be maintained with nitrous oxide and a supplement of an intravenous anaesthetic, then methohexital would be a preferrable choice. Because of the anticipated difficulty of transition from induction to maintenance for longer procedures when the prolonged action of thiopental is no disadvantage, Propanidid cannot be considered superior to thiopental for induction purposes in general. One further grave disadvantage of the agent is the high incidence of postoperative nausea and emesis if it is used as it was in this series. On the other hand, the fact that Propanidid does not have to be prepared prior to administration and is stable in solution is a definite advantage, as are the relative cardiovascular stability and absence of primary respiratory depression. In the entire series, no thrombophlebitis was encountered, and no tissue irritation was seen on the two occasions when a small amount of the substance was inadvertently injected interstitially.

While on balance the experience with repeated injections of this agent has been such that its use under those circumstances cannot be recommended, experience with it in electroshock therapy was quite good. There was little difference between Propanidid and thiopental as far as the procedure was

concerned, but again awakening from Propanidid was faster and there was no hang-over. This was much appreciated by the nursing staff, who could return the patients more quickly to their rooms with less supervision. The psychiatrists were more reserved in their judgment, and some of them felt that in terms of the over-all result of shock treatment there might be some advantage in the longer sleep provided by thiopental. Propanidid administered as a single injection direct into the vein did not cause any thrombophlebitis and was not characterized by any of the untoward side-effects or sequelae that had been present when it was used as a supplement to the maintenance of nitrous oxide anaesthesia. This would seem to indicate that the main value of Propanidid is as a single injection agent for very short surgical procedures. Since the acceptable dose of 5 mg./kg. will only provide a momentarily quiet patient, it would be suitable only on rare occasions in our institution.

Résumé

Le propanidid est un nouvel anesthésique non barbiturique à courte action; il est dérivé de l'acide phényloxyacétique. On l'a utilisé comme agent d'induction et comme complément à l'anesthésie au protoxyde d'azote chez cinquante malades opérées pour curettage utérin, et comme seul agent (en choisissant quelques cas au hasard à la place du thiopentone) pour des cas d'électrochoc en complétant par des petites doses de succinylcholine. D'après notre expérience avec la série des curettages, cet agent produit fréquemment de la rigidité, de la toux, du hoquet, des mouvements incontrôlables, de même qu'une proportion inadmissible de nausées et de vomissements post-opératoires, du moins s'il est administré selon la technique que nous avons utilisée. Nou n'avons pas pu trouver de relation entre le moment de la prémédication et la fréquence de ces effets secondaires; cependant nous avons noté que l'application d'un tube oro-pharyngé diminuait la proportion des anesthésies douces et agréables. Le propanidid est un agent inducteur à action rapide; le réveil est également très rapide sans laisser de malaise. En réalité, le réveil est si rapide que cet agent n'est pas pratique si l'intervention dure plus d'une minute. A cause de cette action si courte, il est probable qu'on ne pourra jamais remplacer le thiopentone par le propanidid comme agent de routine pour les inductions; en effet, son action sera probablement terminée bien avant qu'une anesthésie convenable ne soit produite par l'agent principal. D'un autre côté, cet agent nous a donné entière satisfaction dans un série de cinquante cas d'électrochoc; il est exactement comparable au thiopentone, sauf pour la rapidité du réveil. Dans ces conditions, on n'a noté aucun effet secondaire désagréable. Les avantages du propanidid ont été les suivants: il est en solution stable, et on n'a pas à le préparer immédiatement avant de l'administrer; il produit rarement de l'hypotension; il ne produit pas de dépression respiratoire importante; toutefois une légère dépression peut suivre l'hyperpnée qui se produit toujours au début. Dans aucun cas des deux séries, on n'a observé de thrombo-phlébite, mais après les électrochocs pratiqués sous anesthésie au propanidid, on a observé une certaine faiblesse musculaire.

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