COMPARISON OF AN ULTRASHORT ACTING BARBITURATE (22451) WITH THIOBARBITURATES DURING ANESTHESIA

CHARLES M. GRUBER, JR., M.D., D.Sc. (MED.), V. K. STOELTING, M.D.
ROBERT B. FORNEY, PH.D., PHILIP WHITE, M.D.
MARION DEMEYER, M.D.

OVER two thousand barbiturates have been synthesized and tested in animals in an attempt to find an ultrashort acting, oxygen barbiturate. Compound 22451 is a stereoisomeric mixture of alpha and beta *dl*, 1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbituric acid (fig. 1.) sodium salt. This mixture was made available in sufficient quantity to the Indiana University Medical Center for a detailed study. Several departments were asked to cooperate. The results of this combined research effort furnish the data for this report.

Chemistry and Pharmacology.—Compound 22451 is a white crystalline solid, rapidly and easily soluble in water. It is stable in aqueous

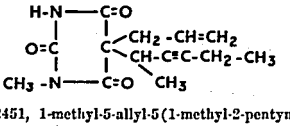

FIG. 1. Compound 22451, 1-methyl-5-allyl-5(1-methyl-2-pentynyl) barbituric acid.

solution at room temperatures for at least six weeks. The *p*H of such solutions, as with other barbiturate salts, is between 10 and 11 (1).

In rats, rabbits, dogs, and monkeys, Compound 22451 is more potent and has a shorter duration of action than thiopental or thioseconal. When injected by vein at hourly intervals, Compound 22451 showed less cumulative action than thiopental or thioseconal. After prolonged anesthesia, recovery time was much more rapid with this

M. L. HICKS, M.D., SAMUEL DOUGHTY, M.D., and SHIRLEY LITTLEFIELD, M.D., of the Department of Anesthesiology, Indiana University School of Medicine; STANLEY M. CHERNISH, M.D., of the Lilly Laboratory for Clinical Research, and RICHARD SOLOMON, B.S., Special Research Fellow sponsored by the Tobacco Industries Research Committee, are also authors of this paper. These names were omitted above because of limitation of space.

Accepted for publication August 31, 1956. Dr. Gruber is in the Lilly Laboratory for Clinical Research, Indianapolis General Hospital, Dr. Stoelting is in the Department of Anesthesiology, Indiana University School of Medicine, Dr. Forney is in the Department of Biochemistry and Pharmacology, Indiana University School of Medicine, Dr. White is in the Department of Neurology, Indiana University School of Medicine, and Dr. DeMeyer is in the Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana.

agent than with either of these thiobarbiturates. The rapid deactivation was dependent, in part, upon liver function (2).

In this report similar findings to those in animals will be demonstrated in humans. The occurrence of hiccups and skeletal muscle tremors are disadvantages to the use of 22451 clinically. However, these undesirable effects have not been seen with alpha, *dl*, 1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbituric acid sodium salt. This isomer is now being tried clinically.

Anesthetic Action of 22451

Method.—Five volunteers received rapid intravenous injections of 100 mg. of 22451 and 500 mg. of thiopental on separate occasions. A second group of five received 100 mg. of 22451 at a rate of 30 mg. per minute and 500 mg. of thiopental at a rate of 110 mg. per minute. Blood samples were taken after the injection was completed. The time at which the specimens were obtained was recorded on a continuous electroencephalographic tracing, described later in this report.

TABLE 1

Differences in Methods Used for Determining Plasma Concentration of 22451 and Thiopental

	Ml. of Plasma	Ml. of $CHCl_3$	Ultraviolet Wave Length
22451	3	75	255
Thiopental	7.5	100	245

The plasma barbiturate levels were determined by ultraviolet spectrophotometry as recommended by Brodie (3). The specific differences in the techniques used for the two drugs are reported in table 1. The volumes of chloroform and time factors used in the extraction were chosen for convenience. This technique extracts essentially all of the barbiturates in the blood specimen. Separatory funnels with standard taper joints were used throughout.

In the extraction, one volume of plasma and one-half volume of Brodie's buffer solution were shaken with the chloroform for ten minutes on a mechanical shaker. After the mixture stood for ten minutes the chloroform layer was removed and filtered through a number 1 Watman filter paper. A measured amount of filtrate, approximately ninety per cent of the original volume of chloroform, was then transferred to a second clean separatory funnel and 4 ml. of 0.25 normal sodium hydroxide added. After shaking ten minutes and standing ten minutes, the aqueous layer was drained into a centrifuge tube and centrifuged for ten minutes. In all cases this layer was clear and colorless. The ultraviolet adsorption was then determined in a Beckman, model D.U., spectrophotometer.

Results.—The results are recorded in figure 2. Data from the

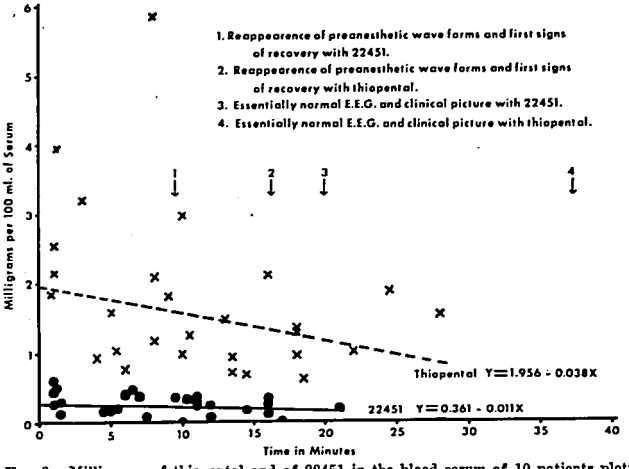

FIG. 2. Milligrams of thiopental and of 22451 in the blood serum of 10 patients plotted against time in minutes. The rate of disappearance is represented by a regression line. Points at which definite clinical and electroencephalographic changes were seen are indicated.

electroencephalographic studies in this paper was used to determine the time intervals at which the changes in the electroencephalogram and clinical picture occurred. These data and the regression lines were used to obtain the values recorded in table 2. This table gives approximate estimates which may be used to compare the anesthetics. It is evident that 22451 is both more potent and shorter in duration than thiopental.

ELECTROENCEPHALOGRAPHIC STUDIES

As shown by Brazier and Finesinger (4), intravenous thiobarbiturates may be associated with rather consistent changes in the electroencephalographic patterns. The changes described are high voltage

TABLE 2

APPROXIMATE PLASMA LEVELS OF 22451 AND THIOPENTAL AT APPEARANCE OF SPECIFIC ELECTROENCEPHALOGRAPHIC AND CLINICAL CHANGES

	22451	Thiopental
Time factors in minutes		
Initial change	9.5	16.2
Complete recovery	20.0	37.5
Difference	10.5	21.3
Serum level factors in mg./100 ml.		
Initial change	0.26	1.34
Complete recovery	0.14	0.53
Difference	0.12	0.81

fast activity with the onset of drug activity becoming intermixed with high amplitude slowing as the level of anesthesia deepens. At deeper levels the amplitude begins to lessen, intermittent periods of flattening occur, and ultimately only very low amplitude slowing remains. The present study was undertaken to determine whether or not the electroencephalogram might be of use in the evaluating of a new barbiturate (22451).

Method.—The electrical activity of the cortex of 10 volunteer human subjects was used to compare the effects of 22451 to those of thiopental sodium. The subjects had normal health and ranged from twenty-one to thirty years of age. Eight were females and 2 were males. The drug was administered by a qualified anesthesiologist, who also maintained a patent airway and administered intranasal oxygen when indicated. Subjects were without previous sedative medication for at least forty-eight hours and each of the 2 drugs was evaluated separately in each subject, allowing at least forty-eight hours for recovery from the initial test. In 5 of the subjects the drugs were administered as rapidly as possible, the average dose of 22451 being 100 mg.; that of thiopental sodium, 500 mg. The 2 drugs were given slowly in 5 subjects, at an average rate of 30 mg. per minute for 22451 and 100 mg. per minute for thiopental sodium; and while the total dose varied to some extent, it averaged about 100 and 500 mg., respectively.

Electroencephalograms were obtained before and during the administration of each drug and were continued without interruption until such time as the subject was able to function normally, unassisted. All recordings were done on a standard Grass, Model III, 8-channel electroencephalograph. One of the channels was used to record the V_1 and V_4 electrocardiographic derivations. The records were then visually analyzed for any changes from the preanesthetic records, all of which were normal.

Clinical levels of anesthesia were estimated (5) and an attempt was made to correlate these with changes in the electroencephalogram. However, this was not found practical because of the telescoping and lack of appearance of some of the usual signs during rapid infusion of these drugs.

Results.—When 22451 was given rapidly, it was associated with an almost explosive onset of high amplitude, rhythmic, synchronous, slow activity arising from all head regions and having a frequency of 2–4 cycles per second. These changes resembled wave forms sometimes associated with types of convulsive disorders but no clinical manifestations of seizures were witnessed. In one patient with organic brain disease and symptomatic epilepsy (not included in the 10 control subjects), there seemed to be an increased number of typical seizures during the administration of 22451, and we have since been informed of 2 patients who did have generalized seizures during the administration of this drug for purposes of surgical anesthesia.

The initial changes with 22451 occurred on the average of thirteen seconds after beginning the infusion. These initial changes were gradually replaced by bursts of mixed fast and slow waves, alternating with periods of quite low voltage slowing, and apnea occurred in association with this. This type of activity, in turn, gave way to a combination of rhythmic 12 to 15-cycle per second synchronous waves, predominating anteriorly, mixed with slower 3 to 6-cycle per second rhythmic waves appearing in a generalized fashion. After an average of seven minutes, the records were noticeably changing gradually back to the preanesthetic characteristics. The typical classical fast activity usually associated with barbiturates was at no time observed during

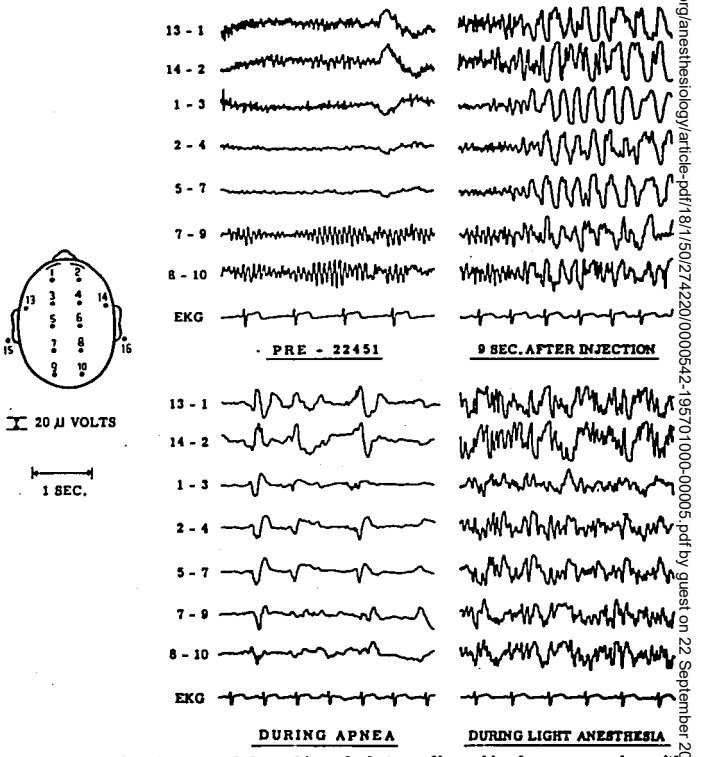

FIG. 3. Successive electroencephalographic and electrocardiographic changes occurring with the intravenous administration of Compound 22451.

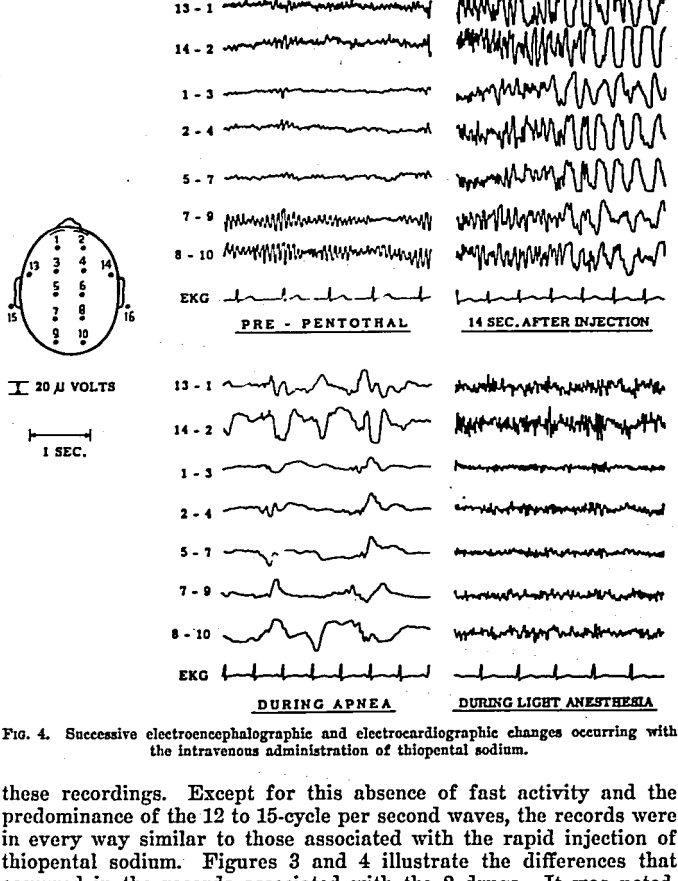

FIG. 4. Successive electroencephalographic and electrocardiographic changes occurring with the intravenous administration of thiopental sodium.

these recordings. Except for this absence of fast activity and the predominance of the 12 to 15-cycle per second waves, the records were in every way similar to those associated with the rapid injection of thiopental sodium. Figures 3 and 4 illustrate the differences that occurred in the records associated with the 2 drugs. It was noted, however, that 22451 acted somewhat more promptly and had a shorter duration of effect both clinically and electrographically when given rapidly.

Clinically, regardless of which drug was used, abrupt loss of consciousness occurred in association with the initial changes in the electrical activity and was quickly followed by a brief period of apnea.

During the ensuing period of unconsciousness, the superficial and deep reflexes persisted and the patient continued to respond to pain by withdrawal. Full consciousness was regained gradually without incident in every case and no serious side-effects were noted. In a few of the subjects minor effects, consisting of mild generalized intermittent tremor, or hiccups, or both were noted.

When the drugs were infused slowly, the sudden initial changes in the records were absent; but otherwise, except for more gradual changes and longer durations, both the clinical and electroencephalographic changes were similar to those noted above. There were fewer minor

TABLE 3

A COMPARISON OF 500 MG. OF THIOPENTAL AND 100 MG. OF 22451 IN 10 PATIENTS*

	Continuous Rapid Injection of		Dose	
	22451	Thiopental	30 mg./min. 22451	110 mg./min. Thiopental
Start of injection to first clinical and EEG signs of change (seconds)	13.0 ±3.9	15.6 ±2.9	24.2 ±7.1	39.2 ±25.9
End of injection to reappearance of preanesthetic wave forms (minutes)	6.7 ±1.7	12.0 ±3.3	12.3 ±4.5	21.4 ±11.6
End of injection to first sign of clinical recovery (minutes)	7.5 ±2.4	12.1 ±4.5	12.3 ±5.0	20.4 ±9.0
Start of injection to clinical and EEG recovery (minutes)	15.0 ±3.0	39.2 ±10.2	29.3 ±14.4	40.0 ±15.1
Number of occurrences of:				
Hiccup	3	1	0	0
Tremor	2	0	3	0

* The body of the table presents the means and the standard deviations for the time of onset and the duration of changes associated with the infusion of these anesthetics. The analyses were accomplished using methods described in Mainland's book (8).

side-effects with the slow administration, but the subjects invariably noted a more persistent lethargy and drowsiness, especially with thiopental sodium. With either drug, whether given rapidly or slowly, no changes were noted in the electroencephalograms which could be considered abnormal or unusual for the existing conditions, except for the absence of the fast activity following the injection of 22451. Table 3 is a composite chart showing some of the time relationships of the changes that occurred.

Electrocardiographic changes were limited to variations in heart rate and occasional inversion of the T wave, the latter presumably in response to myocardial hypoxia following suppression of respiration and reduction in minute volume.

Comparison of Anesthetic Properties Using Double-Blind Technique

Electroconvulsive therapy may be administered repeatedly to conscious or anesthetized patients. A psychiatric service presents an opportunity to compare intravenous anesthetics, when 2 or more are given repeatedly to the same patient. The doses administered need not produce anesthesia in every patient. An attempt was therefore made to determine the dose which would produce anesthesia in 50 per cent (AD_{50}) of a group of patients using the double-blind technique.

Method.—Fifty psychotic, adult, female patients were closely observed during a series of electroconvulsive episodes. The medications listed in table 4 were administered in a random order, rapidly, intravenously in 5 or 6 cc. of water for injection.

TABLE 4

Onset of Anesthesia*

	Dose in Mg.	No. Patients Anesthetized	Onset of Anesthesia in Seconds
Thiopental	125	7	18.1
	150	9	20.7
Thioseconal	125	8	18.8
	150	10	17.9
Compound 22451	15	1	18.0
	30	14	13.5
	50	16	14.1

* Sixteen patients received all 9 treatments. These data were obtained prior to electroconvulsive therapy. The delay before the onset of anesthesia includes only those patients anesthetized.

On each day approximately the same number of patients received each of the drugs. One member of the research team (physicians, nurses, and attendants) administered these treatments; the other members did not know which medication had been given. The latter group made all of the estimates and measurements which are reported herein. Randomization and double-blind testing helped to eliminate biases which might otherwise appear. Only 16 patients received all 9 treatments. Unless otherwise specified the data evaluated were obtained from these patients. In this way each patient served as her own control.

Succinylcholine was given on an arbitrary basis to those patients who had an athletic-type physique. Nine of these 16 patients received 10 or 15 mg. of succinylcholine thirty seconds after each of the anesthetics; the other 7 did not receive any skeletal muscle relaxant or other medication. The succinylcholine was given through the same needle but from a different syringe.

TABLE 5

CHANGE IN RADIAL PULSE AFTER ADMINISTRATION OF ANESTHETICS*

Patient No.	Thiopental	Thioseconal	22451	Blank	Total
1	0	−3	1.3	11	9.3
2	−13	−3	−6.0	−11	−33.0
3	−4	0	−33.0	0	−7.3
4	0	1	−2.7	1	−0.7
5	−6	−5	−6.7	1	−16.7
6	−7	1	2.0	−3	−7.0
7	−2	−3	−3.3	−1	−9.3
8	−2	−2	−0.7	4	−0.7
9	11	4	4.7	6	25.7
10	−8	0	5.3	4	1.3
11	−7	2	−0.7	9	3.3
12	−4	−2	−2.7	−6	−14.7
13	−3	0	−3.3	4	−2.3
14	−2	2	1.3	2	3.3
15	−6	−4	−0.7	−2	−12.7
16	4	0	−2.7	17	18.3
Total	−49	−12	−18.2	36	−43.2

* The radial pulse rate at the wrist was determined just before and for thirty seconds after the intravenous injection of the anesthetic solutions. By subtracting the former from the latter a change in rate was determined. The mean change in beats per minute for the patients receiving all nine treatments is presented in the body of this table.

Thirty seconds after the last injection an electric current from a Medcraft stimulator was applied through temporal electrodes. An initial current of 140 millivolts for 0.4 second was given. If this was insufficient to produce a sustained seizure, a second stimulus of 150 millivolts for 0.5 second was given. Occasionally a current of 160 millivolts for 0.6 second was required. If ineffective stimuli were seen the second and third stimuli followed in rapid sequence.

TABLE 6

ANALYSIS OF THE DATA RECORDED IN TABLE 5*

	ss	*df*	*ms*
Patients	733.07	15	48.87†
Drugs	232.22	3	77.41‡
Thiopental vs. Thioseconal	42.78	(1)	42.78
Compound 22451 vs. Thiopental and Thioseconal	(6.30)	(1)	6.30
Blank vs. Anesthetic	(182.52)	(1)	182.52†
Remainder	647.62	45	14.39
Total	1612.91	63	

* This is an example of the method of analysis used to obtain the data presented in brief in Table 8.

† Significant at $p = 0.001$.

‡ Significant at $p = 0.01$.

TABLE 7

SUMMARY OF THE RESULTS OBTAINED IN THE SIXTEEN PATIENTS WHO RECEIVED ALL NINE TREATMENTS PRIOR TO ELECTROCONVULSIVE THERAPY*

	Thiopental	Thioseconal	22451	Blank
Duration of unconsciousness in minutes	11.3	11.8	9.3	7.3
Duration of apnea in seconds	6.7	7.3	7.6	4.3
Duration of ataxia in minutes	24.7	24.9	24.2	21.0
Number of ineffective first stimuli per sixteen treatments	5.5	5.0	6.3	2.0

* The responses were produced by the anesthetics plus electrical stimulation. The means are presented in the body of the table.

Results.—The lapse of time from the end of injection to the onset of anesthesia was determined. The maximum time allowed was thirty seconds. As can be seen in table 4, the doses chosen were not intended to produce anesthesia in all patients. The two lowest doses of 22451 (15 and 30 mg.) were approximately as potent as the 2 doses of thiopental and thioseconal. By plotting the per cent probability of anesthesia against the log of the doses, it was possible to determine the AD_{50} (dose expected to produce anesthesia in 50 per cent of these patients) for each medication (6). The AD_{50}'s for 22451, thiopental, and thioseconal are 22.3, 138, and 125 mg., respectively. Compound 22451 is about six times as potent as these thiobarbiturates.

The lapse of time before the onset of anesthesia is also presented in table 4. Analysis of the data (table 8) indicates that 22451 produced anesthesia more rapidly than did the thiobarbiturates. No significant differences between thiopental and thioseconal were disclosed (7). Fifty milligrams of 22451 was more potent than the doses of the thiobarbiturates used. An increase in potency may shorten the onset time. In order to remove any bias produced by this difference in potency, data observed with 50 mg. of 22451 was not included in the analysis of the rate of onset of anesthesia.

TABLE 8

MEAN SQUARES ASSOCIATED WITH THE DATA PRESENTED IN TABLES 4 AND 7

	Onset of Anesthesia	Duration of Unconsciousness	Duration of Apnea	Duration of Ataxia
Patients		32.3*	15.8	126.2*
Drugs	140.2*	68.3*	68.9†	53.4†
Thiopental vs. Thioseconal	6.4	2.0	0.2	0.6
Compound 22451 vs. Thiopental and Thioseconal	274.3*	52.2†	0.0*	4.6
Blank vs Anesthetic		150.7*	151.4*	155.9*
Remainder	16.8	6.3	12.0	8.6

* Significant at p = 0.001.
† Significant at p = 0.01.

In the analyses which follow these data are included. The radial pulse was determined immediately before the injection and for the half minute afterwards prior to the administration of the electric stimulation. By subtracting the former rate from the latter a difference was obtained. The differences are presented in table 5. These data are given in detail as an example of the method used for the analyses presented in tables 7 and 8. As seen in table 6, the response of the pulse to the 3 anesthetics was not significantly different (7). However, the difference between the rise in pulse rate with placebo and the fall with the anesthetics would not be expected to occur by chance.

Since electroconvulsive treatment produces apnea and unconsciousness followed by a gradual recovery of motor control, the duration of the effect of the anesthetics could not be determined. The administration of a placebo control allows the evaluation of the effects of the anesthetics when added to electroshock. The duration of unconsciousness was measured from the end of the intravenous injection. Al

TABLE 9

RESULTS OF GIVING SUCCINYLCHOLINE DURING ELECTROCONVULSIVE THERAPY*

	No. of Patients	Unconsciousness in Minutes	Ataxia in Minutes	Apnea in Minutes
Patients receiving succinylcholine	9	10.0	24.7	6.9
Patients not receiving succinylcholine	7	9.6	22.6	9.2

* No significant differences between the treated and untreated patients were found. The body of the table presents the mean values.

patients lost consciousness following each electrical stimulation. The mean durations are presented in table 7. With placebo the lapse of time was usually shorter than that following anesthetic pretreatment. With Compound 22451, the duration was significantly shorter than with the thio-derivatives (table 8).

After the patients had been stimulated, apnea frequently occurred but was of short duration. The mean durations of apnea are presented in table 7. Analysis (table 8) indicates that the periods of apnea are significantly longer with the anesthetics than with placebo. No difference among the anesthetics was observed.

When the period of apnea was over, the patients were transferred to a recovery room. There they remained until motor control had returned sufficiently for them to walk. The mean durations of unconsciousness plus ataxia are presented in table 7. Analysis (table 8) indicates that after placebo, the patients were able to leave the recovery room more promptly than after the anesthetics. No significant differences were seen among these anesthetic agents.

Nine of the 16 patients received succinylcholine and 7 did not. If these 2 groups are comparable, succinylcholine had no significant

effect upon the duration of apnea, of unconsciousness, or of ataxia (table 9). A number of other measurements and estimates were also made. No significant differences among the treatments were observed for the following: resistiveness to treatment; fearfulness toward treatment; blood pressure at the time of the next treatment;

TABLE 10

COMPARATIVE DATA ON PATIENTS RECEIVING PENTOTHAL®, SURITAL® AND COMPOUND 22451 FOR SURGERY

Region	Head and Neck	Thorax	Upper Abdomen	Lower Abdomen	Abdominal Wall	Perineum	Spinal	Limbs	Total		
22451	120	57	17	20	11	197	15	80	525		
Pentothal	108	39	18	30	10	155	10	82	452		
Surital	125	26	9	97	25	165	20	110	577		
Age	−1	−10	−20	−30	−40	−50	−60	−70	−80	80+	Total
22451	4	10	54	82	89	99	83	55	38	11	525
Pentothal	3	54	64	75	81	61	51	34	17	11	452
Surital	0	53	108	88	116	74	55	51	29	3	577
Physical State	1	2	3	4	5	6	7	Total			
22451	170	250	75	3	12	8	7	525			
Pentothal	168	201	62	0	15	6	0	452			
Surital	334	176	22	11	14	15	5	577			
Anesthetic Time	−1/2	−1	−1 1/2	−2	−3	−4	−5	5+	Total		
22451	39	135	64	96	101	42	24	24	525		
Pentothal	43	103	45	83	79	61	15	23	452		
Surital	53	136	98	120	106	34	26	4	577		

Skeletal Muscle Relaxant Used in:	No. Patients	Total Patients
22451	171	525
Pentothal	102	452
Surital	175	577

* Groups of patients who received Pentothal or Surital in combination with 75 per cent nitrous oxide and 25 per cent oxygen were selected at random from earlier time periods for comparison with a group which received Compound 22451. The similarities of these groups are demonstrated in this table.

and undesirable responses such as nausea, vomiting, and bed wetting. Ineffective stimuli occurred less frequently with placebo than with the anesthetics.

CLINICAL STUDIES

Compound 22451 was used intravenously in 650 patients to provide anesthesia for surgery.

Method.—Patients were selected only with reference to ordinary precautions taken in the use of any barbiturate (table 10). They were premedicated with morphine sulfate or Demerol® hydrobromide in

combination with scopolamine hydrobromide or atropine sulfate. The usual ratio of 25:1 was followed. These drugs were given one to one and one-half hours prior to the beginning of anesthesia. A barbiturate (Seconal® sodium) or Nisentil® was frequently administered intravenously, prior to starting the anesthetic after the patients arrived in the operating room.

TABLE 11

ANALYSIS OF THE DATA OBTAINED FROM PATIENTS RECEIVING COMPOUND 22451, PENTOTHAL®, AND SURITAL®*

	Compound 22451 (mg.)	Pentothal (mg.)	Surital (mg.)
Induction:			
Number of patients	361	473	501
Median dose	50	150	200
Mode dose	50	175	250
Mean dose	54.4	156.5	266.4
Standard deviation	±18.8	±69.75	±92.5
95 percent Confidence limits	44.5-64.3	146.5-166.5	213.4-239.4
Intermittent Injection:			
Number of patients	186	349	432
Regression equation			
Slope in mg./hr.	57.4	58.0	153.0
Intersect at 0 hrs.	53.3	338.2	320.4
Standard deviation of slope	±5.3	±11.3	±10.8
95 per cent confidence limits	56.2-58.6	56.1-59.9	151.4-154.6
Continuous Drip ± Intermittent Injection:			
Number of patients	82		
Regression equation			
Slope in mg/hr.	94.9		
Intersect at 0 hrs.	102.5		
Standard deviation of slope	±8.1		
95 per cent confidence limits	92.1-97.7		

* Each group received a different intravenous anesthetic with nitrous oxide and oxygen during routine surgical anesthesia.

The drug was administered in a 1 per cent solution using the intermittent injection technique. This method was accomplished by the insertion of a 3-way stopcock between the needle and intravenous tubing. It was also administered by continuous drip in a 0.1 per cent aqueous solution to more than one hundred patients.

Nitrous oxide and 22451 were the principal anesthetic agents in 525 patients. One hundred and twenty-five patients received 22451 in combination with other anesthetic agents: ether, 6, cyclopropane, 114, and spinal, 4. One patient was given 22451 alone. Metubine iodide or succinylcholine were used in 252 patients to obtain the necessary relaxation.

For purposes of comparison, the records from patients who had been given thiopental or thioseconal with 75 per cent nitrous oxide and 25 per cent oxygen were selected at random from the files of this de-

partment of anesthesiology and examined. These anesthetics were given during previous years and, therefore, the data from the 3 groups of patients may not be comparable.

Results.—A few of the anesthesia records were incomplete and data from these cases could not be used. In the complete reports, 22451 was used for induction of anesthesia (1 per cent solution) on 361 occasions. Although 10 to 200 mg. were used, over 300 of the patients received 40 to 70 mg. The mean and standard deviation of

TABLE 12

COMPLICATIONS RECORDED DURING OR AFTER ANESTHESIAS WITH COMPOUND 22451, PENTOTHAL,® AND SURITAL®*

	Compound 22451	Pentothal	Surital
Number of patients	650	654	619
Respiratory, major	9	7	6
Respiratory, minor	6	6	5
Circulatory, major	8	10	7
Circulatory, minor	6	3	2
Neurological	17	4	9
Nausea and emesis	17	8	51
Gastro-intestinal disturbance	2	3	13
Urinary retention	7	1	16
Genito-urinary disturbance	7	3	10
Total	69	45	119
Deaths in the O.R.	0	3	0
Deaths in the first three days	1	1	1
Shivering and twitching	25	0	0

* The records from patients receiving other anesthetics than nitrous oxide and oxygen are included.

the dose for induction is 54.4 ± 18.3 mg. (8) (table 11). The doses of thiopental and thioseconal used for this purpose were 2.5 and 4 times as large, respectively.

Compound 22451 was administered intermittently with 75 per cent nitrous oxide and 25 per cent oxygen to 187 patients. Thirty-five of these patients were males. The elements of the regression equation (8) for duration and dose are presented in table 11. Similar regression equations for thiopental and thioseconal are included. The equation for 22451 indicates that it was used at a rate of 57.4 mg. per hour.

When 22451 was given by continuous drip (0.1 solution) with 75 per cent nitrous oxide and 25 per cent oxygen, a larger amount was used. The largest dose given was 10 Gm. in six hours. The elements of the regression equation for this method of administration are also presented in table 11. Here 94.9 mg. were given per hour.

Table 12 presents the frequency of complications recorded during the study. Skeletal muscle tremors were seldom considered of sufficient importance to be reported until late in the experimental period.

The staff in anesthesiology had to be warned repeatedly that they must report all unusual responses before notations of tremors appeared in the records.

All patients awoke very promptly when 22451 was discontinued. On awakening they were surprisingly alert.

Discussion

From the study of electrographic changes, it can be concluded that 22451 acts in a similar but not identical fashion to thiopental sodium and other hypnotic barbiturates. It has been postulated that barbiturates owe their depressant action to the ability to inhibit the action of lactic acid dehydrogenase (9). This change, while not preventing the access of oxygen to the brain cells, produces changes in cellular metabolism, the electrical impedance of cell walls, and consequently changes in frequency in the electroencephalogram (10). It may be, therefore, that the action of 22451 is due to an alteration of cellular impedance characteristics unlike that of other barbiturates.

Compound 22451 appears to act like thiopental sodium with respect to pain abolition and is not analgesic, but hypnotic. The subjects would continue to respond to pain, even though apparently deeply unconscious. These responses to pain were not accompanied by any detectable change in the electrographic activity. Thus it appears that these responses follow a pathway at a lower level of the central nervous system and that the cortical cells do not participate in these responses.

The concentrations of 22451 in the peripheral blood, rate of disappearance from the blood, AD_{50}, total dose used in anesthesia, rate of recovery from anesthetic doses and electroencephalographic findings all indicate that 22451 is more potent and has a shorter duration of effect than either thiobarbiturate. This is in keeping with observations made in animals (2). It is free from serious side-effects as determined by the electroencephalogram and clinical use as an intravenous anesthetic.

Conclusions and Summary

Compound 22451 may be used safely as an intravenous anesthetic agent by rapid administration of a single dose, by intermittent administration of successive doses, or by continuous administration of a dilute solution.

Compound 22451 is three to six times as potent as thiopental or thioseconal. This difference in potency appears most pronounced when the solutions are injected rapidly. With rapid administration the AD_{50}'s for 22451, thiopental, and thioseconal were found to be 22.3, 138, and 125 mg., respectively.

Rapid administration of 22451 is associated with an almost explosive onset of high amplitude, rhythmic, synchronous, slow activity arising from all head regions and having a frequency of 2 to 4 cycles

per second. The typical fast activity usually associated with barbiturates was at no time observed during these recordings. Clinically, regardless of which drug was used, abrupt loss of consciousness occurred in association with the initial changes in the electroencephalogram and consciousness returned as the electrical recordings became normal.

Compound 22451 was deactivated in the body more rapidly than was thiopental or thioseconal. Recovery following cessation of anesthesia was most prompt with Compound 22451. The rate of disappearance of 22451 and of thiopental from plasma is 0.011 mg. per minute and 0.038 mg. per minutes respectively. After apneic doses of 22451, complete electroencephalographic and clinical recovery was observed in twenty minutes with a blood concentration of 0.14 mg. per 100 ml. When thiopental was given in equivalent amounts, similar responses occurred in 37.5 minutes and the concentration was 0.53 mg. per 100 ml. of blood.

Electroconvulsive therapy without anesthesia produced significantly shorter periods of apnea, unconsciousness, and ataxia than occurred when anesthesia had been given. The periods of apnea and unconsciousness were shorter following Compound 22451 than following thiopental or thioseconal. The administration of these barbiturate anesthetics prior to electroshock raised the threshold for generalized seizures. The administration of succinylcholine had no significant effect upon the durations of apnea, of unconsciousness, or of ataxia.

Shivering, twitching and hiccups were more frequent with Compound 22451 than with the thiobarbiturates. These symptoms are not sufficiently severe to be alarming.

Investigation of the isomers of Compound 22451 is continuing.

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