A COMPARATIVE CLINICAL AND STATISTICAL STUDY OF THIOPENTAL AND THIAMYLAL IN HUMAN ANESTHESIA *

RALPH M. TOVELL, M.D.,†
Hartford, Connecticut
CHARLES C. ANDERSON, M.D.,‡ MAX S. SADOVE, M.D.,§
Chicago, Illinois
JOSEPH F. ARTUSIO, JR., M.D.,|| E. M. PAPPER, M.D.,¶
New York, New York
CHARLES S. COAKLEY, M.D.,# FERNANDO HUDON, M.D.**
Washington, D. C. *Quebec, Canada*
SCOTT M. SMITH, M.D.,†† AND GEORGE J. THOMAS, M.D.‡‡
Salt Lake City, Utah *Pittsburgh, Pennsylvania*

INTRODUCTION

SINCE the publication of the synthesis of the thiobarbiturates in 1935 (1) and the report of the initial clinical studies (2, 3), a large volume of literature has been written describing the pharmacology, the toxicity, and the clinical application of these intravenous anesthetics. Gradually, the limitations, the indications, and the usefulness of these agents have been established, and now the thiobarbiturates generally are accepted as being among the most satisfactory anesthetic drugs from the standpoint of the patient, the anesthetist, and the surgeon.

Pentothal® sodium (thiopental) rapidly became popular and enjoyed a critical attention shared by few drugs. It is interesting to observe that, of the 18 thiobarbiturates reported in the initial publication, thiopental was selected as the most suitable thiobarbiturate for human anesthesia. Since the original evaluation, many thiobarbiturates have been synthesized and tested for anesthetic effect. The search has been directed primarily toward a thiobarbiturate which

* Accepted for publication March 24, 1955.
† Chairman, Department of Anesthesiology, Hartford Hospital, Hartford, Connecticut.
‡ Department of Anesthesia, Presbyterian Hospital, Chicago, Illinois. (Present address: Samuel Merritt Hospital, Oakland, California.)
§ Head, Division of Anesthesiology, University of Illinois, Chicago, Illinois.
|| Attending Anesthesiologist in Charge, The New York Hospital, New York, New York.
¶ Director, Department of Anesthesia, Presbyterian Hospital, New York, New York.
# Director of Anesthesiology, George Washington University Hospital, Washington, D. C.
** Department of Anesthesiology, Hotel-Dieu, Quebec, Canada.
†† 910 Medical Arts Building, Salt Lake City, Utah.
‡‡ Director, Department of Anesthesiology, St. Francis Hospital, Pittsburgh, Pennsylvania.

is metabolized more rapidly in the body and which would permit even better control of anesthesia.

During most of this search, the opinion of many investigators was that the duration of thiopental anesthesia was due to its rapid metabolism (4–6). Convincing evidence has been presented that the short duration of thiobarbiturate anesthesia is dependent on a relatively rapid redistribution of plasma thiobarbiturate into fat, from which it is slowly liberated and metabolized (7–11). The method of metabolism has not been elucidated completely, but thiopental carboxylic acid has been identified as one of the metabolic products, and the process proceeds relatively slowly (9, 11, 12)—10 to 15 per cent per hour. Based on observations with Pentothal, Surital® (thiamylal), kemithal, and other thiobarbiturates, Brodie's conclusions (9) are that all thiobarbiturates owe their apparent rapid action to this redistribution from plasma to fat. These conclusions are based on specific spectrophotometric analytical methods and have been confirmed by

TABLE 1

NUMBER OF CASES

Hospital	Thiopental	Thiamylal	Total
0 Quebec	235	268	503
1 Hartford	11	106	117
2 New York City	96	86	182
3 Presbyterian—New York City	371	376	747
4 George Washington University	70	121	191
5 Pittsburgh University	14	12	26
6 University of Illinois	96	58	154
7 Presbyterian—Chicago	3	33	36
8 Utah	202	185	387
Totals	1,098	1,245	2,343

radioactive S^{35} tagging methods (11). The concensus of many investigators is that this phenomenon is shared by all thiobarbiturates and that the search for better intravenous anesthetic agents should be directed toward compounds other than the thiobarbiturates.

Following the introduction of surital (thiamylal), considerable medical literature has appeared on its anesthetic effect (13–29). Most published clinical reports on the relative efficacy of thiopental and thiamylal were based on clinical impressions and the conclusions are markedly diversified. The present study was undertaken to test the drugs critically under controlled conditions in various human surgical procedures under ordinary conditions of anesthesia.

METHODS

Nine departments of anesthesia (table 1) in the United States and Canada participated in the study. Thiopental and thiamylal were pre-

pared§§ in ampules identified only by one of 6 code letters. The solution of thiamylal was indistinguishable visually from thiopental. Selection of patients for whom a thiobarbiturate ordinarily would be used was at random. The preoperative condition of the patient, his reactions and complications during induction, his maintenance, and his recovery were recorded on a form containing more than 100 entries.

TABLE 2

WEIGHT

Hospital	Thiopental		Thiamylal		Difference*
	N*	Mean*	N	Mean	
0 Quebec	139	131.8± 2.8	140	139.6±2.8	− 7.8
1 Hartford	8	124.2±11.6	91	143.0±3.4	−18.8
2 New York City	72	139.9± 3.9	54	145.0±4.5	− 5.1
3 Presbyterian—New York City	196	141.7± 2.4	215	145.2±2.2	− 3.5
4 George Washington University	68	136.9± 4.0	115	141.2±3.1	− 4.3
5 Pittsburgh University	14	148.6± 8.8	11	138.3±9.9	10.3
6 University of Illinois	91	150.9± 3.4	49	138.6±4.7	12.3
7 Presbyterian—Chicago	2	175.0±23.3	28	127.9±6.2	47.1
8 Utah	158	137.2± 2.6	151	141.5±2.7	− 4.3
Unbiased estimate of mean*		142.9		140.0	

Analysis of Variance

Source of Variation	D.F.*	Mean Square	F Ratio	Significance*
Between hospitals		2,410	1.04	P>.05
Between drugs within hospitals	9	2,308	2.13	P∼.025
Error	1,584	1,085		
Total	1,601			

* The above headings have the following significance:
N: the number of cases.
Mean: arithmetic mean ± standard error of the mean.
Differences are positive if thiopental is greater; negative if thiamylal is greater.

$$\text{Unbiased estimate of the mean} = \frac{\text{sum of hospital means}}{\text{number of hospitals}}$$

D.F.: Degrees of freedom.
Significance: 0.05 level arbitrarily assumed; if P>0.05, difference is not significant.

Part of the patients received a coded thiobarbiturate for induction only, and the remainder received the drugs for induction and during maintenance, usually with supplementary inhalation anesthesia. The forms were examined for completeness, and those forms which were incomplete were rejected by a group of anesthesiologists ||| who did

§§ By Abbott Laboratories, North Chicago, Illinois.

||| Drs. E. J. Remlinger, Norene B. Hess, Chicago, Illinois, and residents of Dr. Remlinger's staff at Evanston Hospital, Evanston, Illinois.

not participate in the study. The data were tabulated by this group in a form suitable for statistical analysis. The age, the weight, the sex, and a general description of the patient population, the premedication drugs used, the supplementary anesthetic agents and other significant parameters describing the patients anesthetized were tabulated, but do not appear with this report. The data (including the surgical procedures in each group and the ASA code risk) show the distribution of complex surgery and poor-risk patients to be well proportioned between each group.

Appropriate statistical analysis is designed to clarify a mass of data, to record all the information contained in the data, and to esti-

TABLE 3

AGE

Hospital	Thiopental		Thiamylal		Difference
	N	Mean	N	Mean	
0 Quebec	233	41.0± 1.1	267	40.7±1.0	.3
1 Hartford	11	34.7± 5.1	106	45.2±1.6	−10.5
2 New York City	96	47.1± 1.7	86	48.4±1.8	− 1.3
3 Presbyterian—New York City	357	40.4± .9	369	39.8± .9	.6
4 George Washington University	68	41.5± 2.0	115	43.0±1.6	− 1.5
5 Pittsburgh University	14	46.1± 4.5	12	28.4±4.8	17.7
6 University of Illinois	95	49.4± 1.7	58	49.1±2.2	.3
7 Presbyterian—Chicago	2	42.0±11.9	33	45.5±2.9	− 3.5
8 Utah	201	38.7± 1.2	185	38.8±1.2	− .1
Unbiased estimate of mean		42.3		42.1	

Analysis of Variance

Source of Variation	D.F.	Mean Square	F Ratio	Significance
Between hospitals	8	2,840	7.53	.01>P>.001
Between drugs within hospitals	9	377	1.34	P>.05
Error	2,290	282		
Total	2,307			

mate the precision of the data. Information of the type obtained in such a study is subject to certain errors, controllable and uncontrollable. Error is introduced by the variability of interpretation of results, by differences in clinical judgment as to degree of subtle changes, as well as error in recording, etc. However, these errors can be balanced for the purpose of such a study by the equal distribution of error in both drug groups, and biometrics provides accurate methods for the evaluation and the measurement of the factors contributing to error.

The application of elaborate and precise methods of statistical

analysis to such data may be less justifiable than simple analysis to the largest volume of data. However, because of the considerations mentioned above, analysis of the data in this study was approached in several ways. First, the information to be analyzed was pooled across all hospitals, and standard methods of statistics applied. The arithmetic mean and its standard deviation (the standard error of the mean) were calculated, and the "t" test applied to test the significance of the difference in the means. The complications also were pooled, and the probabilities of their occurrence were expressed as percentage incidence. Second, analysis of variance (30–32) was applied to the data and the incidence of complications evaluated by means of the chi-squared test.

TABLE 4

TOTAL DOSE OF INTRAVENOUS ANESTHETIC AGENT/WEIGHT OF PATIENT/TOTAL TIME INDUCTION AND MAINTENANCE

Hospital	Thiopental		Thiamylal		Difference
	N	Mean	N	Mean	
0 Quebec	106	.089±.009	102	.084±.009	.005
2 New York City	19	.156±.020	19	.129±.020	.027
3 Presbyterian—New York City	133	.085±.008	127	.089±.008	−.004
4 George Washington University	63	.109±.011	108	.136±.008	−.027
5 Pittsburgh University	13	.217±.024	11	.157±.027	.060
6 University of Illinois	19	.083± .20	17	.080±.021	.003
8 Utah	120	.124±.008	123	.088±.008	.036
Unbiased estimate of mean		.123		.109	

Analysis of Variance

Source of Variation	D.F.	Mean Square	F Ratio	Significance
Between hospitals	6	.071665	3.39	P>.05
Between drugs	1	.018718	<1	
Interaction	6	.021143	2.71	.05>P>.01
Error	966	.007791		
Total	979			

Tables 2 and 3 shows the weight and the age distribution of the patients anesthetized. The recording of the various procedures applied to these data will serve to illustrate the foregoing discussion. It is apparent that there is considerable difference in the mean values of ages and weights in the participating hospitals; this variation is shown to occur not only among hospital averages but also among the patients receiving the drugs under test. This is reflected in the values for "F" indicated. The value reported as the "unbiased estimate of the mean" is the result of totaling the individual means, and dividing by the number of means (number of hospitals). The discussions above are now brought into focus, and the question proposed as to the effect

of these differences on the conduct of anesthesia. There is no evidence to indicate that a difference of several years of adult age has any relationship to the effect of a drug, and the mean ages are greater for thiopental in some hospitals and greater for thiamylal in others. The same observations pertain to the weights. Table 2 indicates that the weights of patients *within* hospitals between drugs is significantly different, whereas the ages are significantly different *among* hospitals.

Accordingly, it has been considered advantageous to analyze the data of this study with the techniques described, namely, the variance,

TABLE 5

VITAL SIGNS

Period	Drug	Average Value		
		Blood Pressure (mm. Hg)	Pulse (/min.)	Respiration (/min.)
Preanesthetic value	Thiopental	124.1*	88.3*	19.5*
	Thiamylal	127.7	89.6	19.3
	Significance of difference	None	None	None
Induction changes	Thiopental	−6.8†	−2.5	−0.2
	Thiamylal	−6.9	−0.2	−0.3
	Significance of difference	None	None	None
Maintenance changes	Thiopental	+5.0	+1.2	+1.6
	Thiamylal	+6.9	+ .6	+1.2
	Significance of difference	P<0.001	None	None
Recovery changes	Thiopental	−5.0	−0.9	−0.4
	Thiamylal	−5.2	−0.7	−0.5
	Significance of difference	None	None	None

* All figures are unbiased estimates of the mean for all hospitals (see text).
† + and − signs indicate positive or negative net average changes.

the error, and the interaction. On the other hand, it is considered pharmacologically justifiable to view the complications and other objective parameters as additive, since such observations are related to the immediate previous status of the patient and are reducible to individual relative measurable values. The results obtained by either approach do not appreciably alter the conclusions; however, both methods were calculated for the sake of completeness.

RESULTS

Table 1 describes the distribution of cases in the participating hospitals. Table 4 illustrates the second type of analysis of variance in

which the interaction is significant but the difference between drugs is not significant.

Preanesthetic blood pressure, pulse, and respiration, and the changes which occurred in these vital signs during the periods of anesthesia, are tabulated in table 5. For the sake of summarizing

TABLE 6

INDUCTION PERIOD

Amount of Drug to Accomplish	Thiopental (mg.)	Thiamylal (mg.)	Difference	Significance
Nystagmus	156	146	10	None
Inability to open eyes	261	252	9	None
Comparable with Plane I of ether	390	357	33	None
To intubate	475	424	51	0.05>P>0.01
	(mg./lb.)	(mg./lb.)		
Nystagmus	1.11	1.05	0.06	None
Inability to open eyes	1.96	1.81	0.15	None
Comparable with Plane I of ether	2.66	2.49	0.17	None
To intubate	3.66	3.07	0.59	None

TABLE 7

INDUCTION AND MAINTENANCE

	Thiopental	Thiamylal	Difference	Significance
Time (minutes)	72.62	69.62	3.00	None
Total dose (mg.)	847	767	80	None
Total dose (mg./lb.)	6.29	5.92	0.37	None
Total dose (mg./lb./min.)	0.123	0.109	0.014	None

TABLE 8

RECOVERY PERIOD

	Thiopental	Thiamylal	Difference	Significance
Number of cases of induction only	417	416	No	None
Time after anesthesia to:				
Maintain airway	33 min.	34 min.	1	None
React to pain	27 min.	30 min.	3	None
React to touch	35 min.	34 min.	1	None
React to voice	39 min.	39 min.	No	None
Answer questions clearly and intelligently	67 min.	70 min.	3	None

TABLE 9

INDUCTION COMPLICATIONS

	Thiopental	Thiamylal	Difference	Significance of Difference
Time required (minutes)	1.00 ± 0.06	0.95 ± 0.04	0.05	None
Apnea	271/1,154, 23.48%	303/1,283, 23.62%	0.14	None
Duration of apnea (seconds)	24.50 ± 1.01	22.72 ± 0.99	1.78	None
Cyanosis	41/1,154, 3.55%	62/1,283, 4.83%	1.28	None
Laryngospasm	41/1,117, 3.67%	43/1,225, 3.51%	0.16	None
Duration of laryngospasm (seconds)	22.5 ± 3.3	35.0 ± 3.8	12.5	0.01 > P > 0.001
Arrhythmia	19/217, 8.76%	19/172, 11.05%	2.29	None
Hiccough	6/1,154, 0.52%	9/1,283, 0.70%	0.18	None
Swallowing	44/1,154, 3.81%	45/1,283, 3.51%	0.30	None
Retching	10/1,154, 0.87%	6/1,283, 0.47%	0.40	None
Vomiting	9/1,154, 0.78%	4/1,282, 0.31%	0.47	None
Trismus	4/1,152, 0.35%	1/1,281, 0.08%	0.27	None
Stridor	19/1,154, 1.65%	17/1,281, 1.33%	0.32	None

these results in convenient form, the unbiased estimate of the mean ¶¶ is presented as a representative figure, but the figure recorded as the significance of the difference is calculated from analysis of variance, as illustrated in tables 2, 3, and 4.##

¶¶ The term "unbiased estimate of the mean" is a mathematical description of the process used to derive this figure. It does not imply that no bias is introduced. Since the analysis of variance indicates the data are not additive, the figure approximates a mean and is more accurate than the true arithmetic mean summed across all the data. It is introduced only to facilitate tabulation of the data.

Complete statistical data and calculations have been compiled, but for the sake of conciseness are omitted from this publication.

TABLE 10

MAINTENANCE COMPLICATIONS

	Thiopental	Thiamylal	Difference	Significance
Arrhythmia				
Extrasystole	7	7	0	
Auricular fibrillation	2	0	2	
Sinus tachycardia	3	2	1	
Bradycardia	1	1	0	
Other	3	10	7	
Total incidence	16	20		
Total cases reported	368	397		
Per cent of incidence	4.34	5.04	0.70	None
Cyanosis	19/700, 2.7%	28/833, 3.4%	0.7	None

TABLE 11

RECOVERY COMPLICATIONS

	Thiopental	Thiamylal	Difference	Significance
Arrhythmia	2*/736, 0.27%	7/859, 0.81%	0.54	None
Cyanosis	23/735, 3.13%	23/861, 2.67%	0.46	None
Laryngospasm	3/618, 0.49%	4/717, 0.56%	0.07	None
Restlessness and jactitation	51/736, 6.93%	55/859, 6.40%	0.53	None
Coughing	22/736, 2.99%	28/859, 3.26%	0.27	None
Hiccough	7/736, 0.95%	3/859, 0.35%	0.60	None
Trismus	7/735, 0.95%	4/861, 0.46%	0.49	None
Delirium	10/735, 1.36%	6/861, 0.70%	0.66	None

* The numerator of each fraction represents the occurrence of the complication in the number of recorded observations listed in the denominator.

TABLE 11—*Continued*

	Thiopental	Thiamylal	Difference	Significance
Nystagmus	11/735, 1.50%	6/861, 0.70%	0.80	None
Nausea	80/734, 10.90%	117/861, 13.59%	2.69	None
Vomiting	84/735, 11.43%	74/861, 8.59%	2.84	None
Sneezing	0/735, 0.0 %	1/859, 0.12%	0.12	None
Retching	8/735, 1.09%	4/861, 0.46%	0.63	None
Pallor	19/735, 2.59%	20/861, 2.32%	0.27	None
Headache	24/735, 3.27%	45/861, 5.23%	1.96	None
Ataxia	2/735, 0.27%	4/861, 0.46%	0.19	None
Thrombosis at site of injection	0/735, 0.0 %	0/861, 0.0 %	0.0	None

TABLE 12

OTHER RECOVERY COMPLICATIONS

Complication	Thiopental	Thiamylal	Significance
Dizziness	0/735	24/861, 2.79%	P ~ 0.001
Fever	5	5	None
Prolonged restlessness	0	1	None
Irregular pulse	0	1	None
Twitching of muscles	0	1	None
Herpes	0	1	None
Prolonged hypertension	0	1	None
Urticaria	0	1	None
Circulatory collapse	0	1	None

It will be noted that the observations tabulated by some hospitals are so few that their contribution to the results could be questioned. It has been found that these entries do not affect the conclusions based on analysis of variance and they are included for completeness.

Table 6 describes the amount of drug used in the induction period expressed as milligrams and as milligrams per pound of body weight. Table 7 summarizes the time and the dosage for the thiobarbiturates used during induction and maintenance, and table 8 indicates the time required for the patients to react to the listed endpoints. Tables 9, 10, and 11 show the incidence of complications in the induction period, the maintenance period, and the recovery period, respectively. Table 12 summarizes the complications that occurred during maintenance.

DISCUSSION

The results of this investigation, as summarized in tables 5, 6, 7, and 8, and the incidence of complications, summarized in tables 9, 10, 11, and 12, indicate little difference in effect of thiopental and thiamylal in routine human anesthesia. The only differences which have statistical significance are the greater elevation of blood pressure during the maintenance period with thiamylal, a borderline greater amount of thiopental to accomplish induction to the endpoint of "to intubate" (see table 6), which disappeared when the amount of drug per pound and the amount of drug per pound per minute was calculated, a longer duration of laryngospasm for thiamylal, and a higher incidence of dizziness during recovery for thiamylal.

The evaluation of subtle differences in similar drugs based on clinical impression can be misleading. Not only may unconscious bias arise, but, also, long familiarity with a drug justifies more confident administration. This confidence may yield higher dosage schedules, for example, than the careful titration of effect with an unfamiliar drug. These factors are recognized by Gain (14) and his associates, who state that their conclusions "merely record our clinical impressions" and that an "accurate comparison" is contemplated. The only direct comparisons of thiopental and thiamylal reported are those of Lorhan (21) and Tuohy (19), and reference will be made to the results of these investigators.

In general, the results of the present study are in agreement with the clinical observations of Dillon (16), Lorhan (21), Tuohy (19), Kirchof (15), Griffith (17), Stephen (29), Spencer (23), and Littlefield (24), and in some regards are contrary to the clinical impressions of Gain (14), Rovenstine (13), Lund (25, 26), Clarke (20), Phillips (27), and Wall (28). Since, in most reports of clinical comparisons of the 2 drugs, reported differences are characterized by the qualification "seems to be" or "apparent," this investigation was undertaken to compare thiamylal and thiopental with regard to incidence of laryngospasm, cardiac toxicity, potency, and more rapid recovery from anesthesia.

The incidence of laryngospasm recorded in the medical literature shows marked variation, not only with the thiobarbiturates, but also among investigators and drugs. Dillon (16) reports an incidence of

24 in 700 patients (3.4 per cent) receiving thiamylal (actual figure in the report is 0.34 per cent, an obvious typographical error). Lorhan (21) reports an incidence of 3 cases of laryngospasm in 103 patients (2.9 per cent) receiving thiamylal alone, and 4 cases of laryngospasm in 200 patients (2.0 per cent) receiving thiopental. Rovenstine (13) reports an incidence of 8.0 per cent in 1,200 patients receiving thiamylal, and Spencer (23) reports less than 1 per cent receiving thiamylal in 300 cases. The present study shows no significant difference in the incidence of laryngospasm with thiamylal and thiopental (see table 9). However, contrary to the reports of Dillon (16), Rovenstine (13), Gain (14), and Lund (26), the duration of laryngospasm is found significantly longer in duration with thiamylal than with thiopental ($P < 0.01$, table 9). Littlefield (24) noted an incidence of 28 cases of laryngospasm in 1,000 cases with thiamylal (2.8 per cent), 25 of which were reported as severe and 3 as mild.

The contribution of thiobarbiturates to cardiac arrhythmia is more difficult to evaluate because of the relatively inefficient methods of measuring preoperative cardiac reserve, of the important influence of asphyxia, and of the trauma of intubation. Stephen (33) recently summarized the previous animal work relating to the cardiovascular effects of the thiobarbiturates (34–37) that there might be some direct effect on the myocardium and the lack of effect in humans noted by Volpitto (38). He demonstrated that the rate of injection—as in the rapid induction technique—produced a high incidence of arrhythmia, whereas slow induction revealed no electrocardiographic changes. Gruber (39) also reported the differences in effect of thiobarbiturates when administered to human beings and experimental animals. In comparing thiopental and thiamylal, Stephen (33) noted a statistically greater incidence of cardiac arrhythmias with thiopental than with thiamylal when administered rapidly with a muscle relaxant. On the other hand, Rosner (40) described reduction in electrocardiographic disturbances when thiopental was used over the incidence of disturbances during induction in routine techniques without thiopental.

In the present study, composed of both rapid induction and slow induction, the results show no statistical significance to the difference between the 2 drugs. The data for induction are totaled in table 9, and for recovery in table 11. The totals and the incidence of the various forms of arrhythmia are summarized in table 10. No incidence of precipitous hypotension was encountered as reported by Spencer (23) and Clarke (20). Statistically, the incidence of bradycardia with thiamylal as reported by Lorhan (21) was found not significant in the present series. One case of protracted hypertension was encountered with thiamylal similar to that described by Spencer (23), but which did not resolve in precipitous hypotension. Reference to table 5 shows that the only significant difference was in the average decrease in blood pressure with thiamylal during the maintenance pe-

riod. We are in accord with the views of Volpitto (38), Seevers (36), and Stephen (33) that the influence of asphyxia with thiobarbiturates is more important in the clinical application of these drugs than a direct effect on the myocardium. In this connection, the respiratory depression encountered in this series, as indicated by the incidence of apnea and the duration of apnea in the induction period (table 9), shows extremely little difference.

The comparative potencies of drugs must be related either to some drug as a standard, or to each other for relative effect. The amount of drug required to produce an effect, or the duration of effect produced by administration of an equivalent dosage, can be selected for the comparison. In the most commonly quoted animal experiment relative to the potencies of thiopental and thiamylal, Seevers *et al.* (41) used both approaches to determine the relative potencies of thiopental and thiamylal. They reported that, at a dosage level of 25.0 mg./kg. (dogs), the mean duration of anesthesia for thiopental was 74.4 minutes and 132.2 minutes for thiamylal. 15.0 mg./kg. of thiopental and 10.0 mg./kg. of thiamylal was necessary to produce an average sleeping time of approximately 26.0 minutes. In the present study, dosage of 6.29 mg./lb. (13.84 mg./kg.) of thiopental and 5.92 mg./lb. (13.02 mg./kg.) of thiamylal was required to produce a sleeping time of 72.62 minutes for thiopental and 69.62 minutes for thiamylal. There is no statistical difference between 6.29 mg./lb. and 5.92 mg./lb. nor between 72.62 minutes and 69.62 minutes. We have not considered the time required for induction to any of the endpoints as reliable, since the average time is very short and the endpoint broad.

The differences among species have been reported (39, 45, 47), as well as the differences among drugs in the same species (47). Richards (46) has shown that, in rabbits, thiamylal is shorter acting than thiopental with an equal fraction of the fatal dose. In monkeys, thiamylal is almost twice as long acting as thiopental with a dosage of 25 mg./kg. (46). Kelly (42) has demonstrated that plasma levels for thiamylal and thiopental are similar and concluded that the rate of detoxification of the drug is the same regardless of potency. However, Kelly (42) utilized the work of Jailer and Goldbaum (4), which has been shown (7, 8) to be unable to differentiate between thiopental and the inert thiopental carboxylic acid degradation product. The work of Kelly (42) is used to support the observations of Seevers (41), and this work must be reviewed in light of the observations by Brodie (8, 9) that all thiobarbiturates behave similarly in distribution into fat. The difficulties of interpretation of the relative potencies are well illustrated in the work of Barran and Wylie (43), who show that, in a controlled clinical experiment on volunteers, evidence was obtained to indicate that thiamylal is more potent than thiopental and conclude that recovery from a given effect is slower following thiamylal than following thiopental. Perhaps the most effective clinical im-

pression as to the relative potencies of thiamylal and thiopental is that of Lundy *et al.* (44), who report that, although use of thiamylal has proved satisfactory, the assignment of definite advantages to either is difficult because their action is so similar.

Regardless of the relative potencies in dogs, the evidence obtained in this series indicates that there is no significant difference in the potencies of the 2 drugs in humans. This observation is in agreement with the work of Kirchhof (15), Tuohy (18), Dillon (16), and others (17, 21, 24).

Recovery time for thiamylal and thiopental is related intimately to the potency of the drugs and to the cumulative effects. The work of Seevers (41) offers convincing evidence that thiamylal is less cumulative in the dog; on the other hand, Brodie (8, 9) has demonstrated that pentobarbital is metabolized at very nearly the same rate as thiopental in the dog. Swanson (47) has demonstrated that species differences exist in the response, not only among species but also between thiopental and thiamylal. The fallacy of extrapolation to human effect becomes apparent. None of the reports cited has tested the problem of recovery and cumulative action critically in the human; all quote the animal experimentation and unjustifiably conclude that thiamylal may be more potent. However, in the present study, frequent conjecture as to the identity of the coded ampules of drugs was entertained by the participating physicians, and in no case were the guesses more correct than expected by chance variation. Table 8 summarizes the average time required to react to the various endpoints, and emphasizes the remarkable similarity in recovery time.

Postoperative nausea and vomiting has been reported in a large percentage of patients receiving thiamylal by several investigators. For example, Lorhan (22) comments on the incidence of 30 (15 per cent) in his series of 200 cases. Littlefield (24) reports 44 cases (44 per cent) of nausea and vomiting in 100 cases receiving thiamylal; Tuohy (19) reports a slightly higher incidence with thiamylal over thiopental. The present series shows no significant difference in the incidence of nausea and vomiting.

A surprising result of the study reveals a statistically significant greater incidence of post-recovery dizziness with the use of thiamylal. This effect is summarized in table 12, with complications of doubtful relationship to anesthesia.

CONCLUSIONS

In human anesthesia, there is no statistically significant difference between thiopental and thiamylal with regard to potency, cardiotoxicity, respiratory depression, incidence of laryngospasm, or recovery time.

Four statistically significant differences between thiopental and

thiamylal which probably are of no clinical importance have been noted: (a) a greater duration of laryngospasm with thiamylal, (b) a greater elevation of blood pressure during the maintenance period for thiamylal, (c) thiamylal shows a statistically significant higher incidence of dizziness in the recovery period, and (d) a greater amount of thiopental was used to accomplish the endpoint of "intubation" when expressed as total amount of drug. The difference expressed in (d) disappeared when the amount of thiopental per pound and the amount of thiopental per pound per minute was determined. No significant difference appeared in the other endpoints selected for the induction period.

No apparent differences of clinical significance have been observed between thiopental and thiamylal in human subjects.

SUMMARY

A blind study involving 1,098 thiopental and 1,245 thiamylal human anesthesias under routine conditions of anesthesia is presented with a statistical analysis of the effects of the drugs. Particular attention has been focused on the relative potencies, occurrence of laryngospasm, cardiotoxic effects, respiratory depression, recovery time, and cumulative effect. The results of other investigators relative to these points are mentioned and compared with the data obtained in this study. Discrepancies and similarities are discussed.

REFERENCES

1. Tabern, D. L., and Volwiler, E. H.: Sulfur-containing Barbiturate Hypnotics, J. Am. Chem. Soc. **57**: 1961 (Oct.) 1935.
2. Lundy, J. S., and Tovell, R. M.: Annual Report of 1934 of Section on Anesthesia: Including Data on Blood Transfusion, Proc. Staff Meet. Mayo Clin. **10**: 257 (April 24) 1935.
3. Lundy, J. S.: Intravenous Anesthesia: Preliminary Report of Use of Two New Thiobarbiturates, Proc. Staff Meet., Mayo Clin. **10**: 535 (Aug. 21) 1935.
4. Jailer, J. W., and Goldbaum, L. R.: Studies on Plasma Concentration and Tissue Distribution of Sodium Pentothal (Sodium Ethyl [1-Methyl-Butyl] Thiobarbiturates), J. Lab. & Clin. Med. **31**: 1344 (Dec.) 1946.
5. Shideman, F. E.; Kelly, A. R., and Adams, B. J.: Role of Liver in Detoxication of Thiopental (Pentothal) and Two Other Thiobarbiturates, J. Pharmacol. & Exper. Therap. **91**: 331 (Dec.) 1947.
6. Dorfman, L., and Goldbaum, L.: Detoxification of Barbiturates, J. Pharmacol. & Exper. Therap. **90**: 330 (Aug.) 1947.
7. Mark, L. C.; Bernstein, E.: Burns, J. J.; Lief, P. A., and Brodie, B. B.: Comparison of Physiological Disposition and Metabolic Transformation of Nembutal and Pentothal, Fed. Proc. **10**: 322 (March) 1951.
8. Brodie, B. B.; Mark, L. C.; Papper, E. M.; Lief, P. A.; Bernstein, E., and Rovenstine, E. A.: Fate of Thiopental in Man and a Method for Its Estimation in Biological Material, J. Pharmacol. & Exper. Therap. **98**: 85 (Jan.) 1950.
9. Brodie, B. B.: Physiological Disposition and Chemical Fate of Thiobarbiturates in Body, Fed. Proc. **11**: 632 (June) 1952.
10. Bollman, J. L.; Brooks, L. M.; Flock, E. V., and Lundy, J. S.: Tissue Distribution with Time after Single Intravenous Administration of Pentothal Sodium (Sodium Ethyl [1-methyl-butyl] and Pentothal S^{35} Thiobarbiturate, Anesthesiology **11**: 1 (Jan.) 1950.

11. Taylor, J. D.; Richards, R. K., and Tabern, D. L.: Distribution of Radioactvie S^{35} of Thiopental (Pentothal) in Rabbit and Cat, Anesth. & Analg. **29**: 101 (March–April) 1950.
12. Tabern, D. L.; Taylor, J. D., and Gleason, G. I.: Radioisotopes in Pharmaceutical and Medical Studies, Nucleonics **7**: 40 (Dec.) 1950.
13. Helrich, M.; Papper, E. M., and Rovenstine, E. A.: Surital Sodium: New Anesthetic Agent for Intravenous Use; Preliminary Clinical Evaluation, Anesthesiology **11**: 33 (Jan.) 1950.
14. Gain, E. A.; Yates, M.; Hoar, Z., and Watts, E. H.: Surital Sodium: Clinical Impressions of New Thiobarbiturate for Intravenous Anesthesia, Canad. M.A.J. **64**: 32 (Jan.) 1951.
15. Kirchhof, A. C.: Clinical Evaluation of Surital, West. J. Surg. **59**: 90 (Feb.) 1951 .
16. Dillon, J. B., and Denson, J. S.: Clinical Trial of Surital Sodium, New Intravenous Barbiturate; Report of Seven Hundred Cases, Ann. West. Med. & Surg. **4**: 172 (April) 1950.
17. Griffith, H. R.: New Aanaesthetic Drugs, Canad. M.A.J. **63**: 533 (Dec.) 1950.
18. Tuohy, E. B.: Progress in Anesthesiology, Postgrad. Med. **8**: 156 (Sept.) 1950.
19. Dornette, W. H. L., and Tuohy, E. B.: Clinical Trial of Surital Sodium in 1200 Cases of General Anesthesia, Anesth. & Analg. **30**: 159 (May–June) 1951.
20. Clarke, M. T.; Walton, C. H., and Bewersdorf, H. L.: Clinical Experience with Surital Sodium: Preliminary Report, Anesth. & Analg. **31**: 73 (March–April) 1952.
21. Lorhan, P. H.; Guernsey, G., and Devine, M. M.: Surital Sodium: Clinical Use, J. Kansas M. Soc. **52**: 525 (Nov.) 1951.
22. Lorhan, P. H., and Devine, M. M.: Surital Sodium: Comparison with Pentothal Sodium, J. Kansas M. Soc. **52**: 528 (Nov.) 1951.
23. Spencer, W. A., and Coakley, C. S.: Clinical Impressions of New Intravenous Barbiturate, Surital Sodium, M. Ann. District of Columbia **20**: 59 (Feb.) 1951.
24. Littlefield, P. A.; Stoelting, V. K., and Graf, J. P.: Clinical Evaluation of Surital Sodium, J. Indiana M. A. **44**: 1105 (Nov.) 1951.
25. Lund, P. C.: New Intravenous Anesthetic Agent, Am. J. Surg. **81**: 637 (June) 1951.
26. Lund, P. C.: Sodium Surital Intravenous Anesthesia: 6000 Consecutive Cases, Anesth. & Analg. **33**: 86 (March–April) 1954.
27. Phillips, H. S.: Some Clinical Observations on Use of Surital Sodium in Combination Anesthesia, Anesth. & Analg. **32**: 56 (Jan.–Feb.) 1953.
28. Wall, R. L.: Clinical Impressions Gleaned from Use of New Intravenous Anesthetic, Surital Sodium, North Carolina M. J. **12**: 505 (Oct.) 1951.
29. Stephen, C. R., and Martin, R.: Clinical Experience with Surital Sodium in Anesthesia, North Carolina M. J. **12**: 501 (Oct.) 1951.
30. Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh, Oliver & Boyd, Ltd., 1925.
31. Snedecor, George W.: Statistical Methods Applied to Experiments in Agriculture and Biology, ed. 4. Ames, Iowa, The Collegiate Press, Inc., 1946.
32. Fisher, Ronald A., and Yates, Frank: Statistical Tables for Biological, Agricultural and Medical Research, rev. ed., London, Oliver & Boyd, Ltd., 1948.
33. Stephen, C. R.; Martin, R., and Nowill, W. K.: Cardiovascular Reactions to Surital, Pentothal or Evipal Combined with Muscle Relaxants or Rapid Anesthesia Induction, Anesth. & Analg. **32**: 361 (Nov.–Dec.) 1953.
34. Gruber, C. M.; Haury, V. G., and Gruber, C. M.: Cardiac Arrhythmia, Characteristic Effect of Thiobarbiturates as Influenced by Changes in Arterial Blood Pressure, J. Pharmacol. & Exper. Therap. **63**: 193 (June) 1938.
35. Kohn, R., and Lederer, L.: Pentothal Studies with Special Reference to EKG, J. Lab. & Clin. Med. **23**: 717 (April) 1938.
36. Woods, L. A.; Wyngaarden, J. B.; Rennick, B., and Seevers, M. H.: Cardiovascular Toxicity of Thiobarbiturates: Comparison of Thiopental and Surital in Dogs, J. Pharmacol. & Exper. Therap. **95**: 328 (March) 1949.
37. Gruber, C. M.; Gruber, C. M., Jr., and Lee, K. S.: Study of Effect of Thiobarbiturates on Cardio-vascular System, Arch. Internat. Pharmacodyn **91**: (Sept. 15) 1952
38. Volpitto, P. R., and Marangoni, B. A.: EKG Studies During Anesthesia with Intravenous Barbiturates, J. Lab. & Clin. Med. **23**: 575 (March) 1938.
39. Gruber, C. M.: Barbiturates and Thiobarbiturates, J.A.M.A. **117**: 1147 (Oct. 4) 1941.

40. Rosner, S.; Newman, W., and Burstein, C. L.: EKG Studies during Endotracheal Intubation; Effect during Anesthesia with Thiopental Combined with Muscle Relaxant, Anesthesiology **14**: 591 (Nov.) 1953.
41. Wyngaarden, J. B.; Woods, L. A.; Ridley, R.; Seevers, M.: Anesthetic Properties of Surital and Certain Other Thiobarbiturates in Dogs, J. Pharmacol. & Exper. Therap. **95**: 322 (March) 1949.
42. Kelly, A. R., Shideman, F. E., and Adams, B. J.: Comparison of Blood Levels of Thiopental, Surital and Thioethamyl in Dog, Fed. Proc. **7**: 233 (March) 1948.
43. Barran, D. A. N., and Wylie, W. D.: Clinical Trial of Sodium Thioquinalbarbitone: New Barbiturate, Anaesthesia **6**: 202 (Oct.) 1951.
44. Lundy, J. S.; Adams, R. C.; Seldon, T. H.; Pender, J. W.; Faulconer, A., Jr.; Paulson, J. A.; Ridley, R. W.; Osborn, J. E., and Courtin, R F.: Annual Report for 1949 of Section of Anesthesiology, Proc. Staff. Meet., Mayo Clin. **25**: 553 (Sept. 27) 1950.
45. Lamson, P. D.; Greig, M. E., and Hobdy, G. J.: Modification of Barbiturate Anesthesia by Glucose, Intermediary Metabolites and Certain Other Substances, J. Pharmacol. & Exper. Therap. **103**: 460 (Dec.) 1951.
46. Richards, R. K.: Personal Communication.
47. Swanson, E. E.: Sodium-5-Allyl-5-(Methylbutyl)-2-Thiobarbituric Acid, Short-Acting Anesthetic, J. Pharm. & Pharmacol. **3**: 112 (Feb.) 1951.