Methohexital and Its Effect on Liver Function Tests

A Comparative Study

N. M. Bittrich, M.D., A. V'R. Kane, M.D., R. E. Mosher, Ph.D.

METHOHEXITAL (Brevital), an ultrashort-acting intravenous barbiturate, two and one-half to four times as potent as thiopental or thiamylal,[1-6] is now available for routine clinical use. The duration of action of methohexital is shorter than thiopental by one-half to two-thirds,[2,4] and its accumulation properties are less than those of thiopental, even over three or four hours of use.[2,7] Coupled with the brevity of action and decrease in accumulation of methohexital is a more rapid rate of disappearance from the plasma. This rate is 15 to 19 per cent per hour for methohexital[8] and 5 to 15 per cent per hour (average of 7½ per cent per hour after diffusion equilibrium has been established) for thiopental.[9]

It has been established[7] that the liver plays the major role in the detoxification of methohexital. Thiopental also depends on the liver for detoxification. Thiopental produces depression in hepatic function tests with the usual clinical doses.[10] Patients with liver damage show a decreased ability to metabolize thiopental. However, patients can still adequately metabolize thiopental with only a small amount of functional liver tissue.[9, 11-14]

Since the deactivation of methohexital is more rapid than thiopental and thiamylal,[2] the question arises as to whether there is impairment of hepatic function with methohexital. It is the purpose of this study to answer this question.

Method

The liver function of one-hundred fourteen patients was studied preoperatively by means of the sulfobromophthalein (BSP) retention,[15] alkaline phosphatase,[16] inorganic phosphate,[17] thymol turbidity,[18] serum glutamic oxalacetic transaminase (SGO-T),[19] and cephalin-cholesterol flocculation[20] tests. On the third postoperative day the above studies were repeated. The upper limits of normal for these tests were taken to be as follows:

- Thymol Turbidity: Less than 5 units.
- Serum Glutamic Oxalacetic Transaminase (SGO-T): Less than 40 units.
- Cephalin-cholesterol Flocculation: Negative at 24 and 48 hours.
- Alkaline Phosphatase: Less than 6 units.
- Inorganic Phosphate: Less than 4.7 units.
- Sulfobromophthalein (BSP) Retention: Less than 5 per cent retention in 45 minutes at the 5 mg./kg. dose level.

These patients were given meperidine or morphine and scopolamine or atropine as premedication one and one-half hours before induction of anesthesia. A phenothiazine derivative, either prochlorperazine 5 mg. or promethazine 12.5 to mg. 25, was also given. The patients were anesthetized with 1 per cent methohexital, 2½ per cent thiopental, or 2½ per cent thiamylal, administered by intermittent injection according to patient requirement. Nitrous oxide and oxygen were administered at a flow rate of 4 liters per minute and 1½ liters per minute, respectively. When endotracheal intubation was used, a single dose of succinylcholine (60 mg. to 100 mg.) was administered intravenously. No other drugs were given.

We recorded the type and duration of anesthesia, total dosage, intervals of administration, and interval dose of barbiturate. The patient's age, weight, condition, and type of surgical procedure were also noted.

Results and Discussions

Of one hundred and fourteen patients studied, 77 received methohexital, 26 thiopental, and 11 thiamylal. The majority of

Accepted for publication October 2, 1962. Drs. Bittrich and Kane are in the Department of Anesthesiology, Providence Hospital, and Dr. Mosher is in the Department of Research, Providence Hospital, Detroit, Michigan.

patients in each group had breast or thyroid surgical procedures. The distribution of patients having other types of surgical procedures was approximately equal for the three groups. However, almost five-sixths of the patients who had orthopedic surgical procedures received methohexital. In over one-third of the patients, all the preoperative liver function tests were normal. The remainder had one or more tests above the upper limits of normal and were considered to be "abnormal." The average duration of anesthesia and weight and age of the patients for each of the three groups closely approximated the average for the entire series. The average total dosage of thiopental as compared to methohexital was two-to-one. This rate was slightly less for thiamylal.

General Gross Comparison

As changes in alkaline phosphatase and inorganic phosphate levels were negligible for most of the patients, these results were not used in this comparison. Comparison of the sum effect on the five remaining liver function tests was made initially on a qualitative basis for patients receiving different drugs and between "normal" and "abnormal" patients receiving the same drug.

In a given comparison, each patient was matched according to weight, type of surgical procedure, physical condition, age, and duration of anesthesia with a similar patient from the opposite group. These "matched" pairs were then assembled into opposing groups. Patients who could not be matched with a similar patient in the opposite group were not considered. If one member of a matched pair had no value for one of the function tests, the other member's corresponding test result was excluded from consideration. This method of matching patients into opposing groups tends to compensate for many major variables, since it assured that the groups were sufficiently alike to make comparisons valid.

The "incidents" of increases in test values were determined for each patient. Any elevation above a preoperative test result was considered to be an "incident" of increase. The number of incidents of increased tests was tallied for each group and the difference between the "matched" groups was expressed in the differences in the totals. There was no significant difference in the incidents of increased tests between "normal" and "abnormal" patients receiving methohexital. The same was true for thiopental. When comparison was made between "normal" patients receiving methohexital and those receiving thiopental no significant difference was found. Comparison of these two drugs in "abnormal" patients showed no difference.

A comparison between the "normal" and "abnormal" patients receiving thiamylal was impractical because of the small number of patients. A comparison was made between patients receiving methohexital and those receiving thiamylal. The matched pairs forming these groups were matched as "normal-to-normal" and "abnormal-to-abnormal." No difference in the incidents of increased tests was found between these matched groups.

Detailed Comparisons

In table 1, the initial detailed comparison using matched groups of patients is presented. These were the same previously-described groups of patients. The average drug dosage, patient weight, and duration of anesthesia are indicated. The increment of change between the preoperative and postoperative tests was determined for each case. For each test the amount of change was averaged for the groups, and comparison was then made between the matched groups by noting the differences in the amount of average change for each type of test.

In each instance the thymol turbidity test showed a decline from the preoperative level. This was true for all comparative groups in table 1. Furthermore, the average decline was greater in "abnormal" patients as opposed to "normal" patients who received the same barbiturate. To exclude the possibility that this decline in thymol turbidity was a peculiarity of the matching technique, the average change associated with each drug was calculated for the entire series of unmatched patients. The decrease still occurred and was greatest in those patients who received methohexital and thiamylal. Patients receiving thiopental had only half the decrease found for the other two drugs. Again, "abnormal" patients had a greater decrease than "normal" patients receiving the same compound. This phenomenon is unexplained but can hardly be interpreted as meaning that all three drugs improved liver function.

The average increase in cephalin-cholesterol flocculation at 24 hours and 48 hours was less than one plus in all matched groups. "Normal" patients who received methohexital had the highest average change in the 48 hour test. Even here, the associated change in the cephalin-cholesterol flocculation test was less than one. Since thymol turbidity and cephalin-cholesterol flocculation changes had no relationship to the amount of drug or to the duration of anesthesia (as described later) changes in these tests can hardly be significant.

The changes in BSP and SGO-T were of greater numerical value than the changes in the other two tests and merit a more complete

TABLE 1. Comparison of Three Barbiturates by Increment of Change in Liver Function Tests

Type Patient and Barbiturate Comparison	Number Matched Pairs	Average Duration (minutes)	Average Weight (kg.)	Average Dose (mg.)	BSP Retention (per cent)	24-Hour Ceph. Floc. (units)	48-Hour Ceph. Floc. (units)	Thymol Turbidity (units)	SGO-T (units)
"Normal" patients receiving Methohexital		94.3	61.7	519.3	+3.15	+.27	+.80	− .77	+ 1.7
Compared to:	15								
"Abnormal" patients receiving Methohexital		96.7	61.9	562	+3.79	+.4	+.47	− .90	+ 3.6
"Normal" patients receiving thiopental		76.7	69.8	1275	+5.75	0	+.33	− .14	+10.7
Compared to:	6								
"Abnormal" patients receiving thiopental		90.8	69	995.8	+3.31	+.33	+.33	− .61	+ 2.1
"Normal" patients receiving Methohexital		88.3	64.9	570	+5.11	+.17	+.83	− .73	− 1.34
Compared to:	6								
"Normal" patients receiving thiopental		76.7	69.8	1275	+5.75	0	+.33	− .14	+10.7
"Abnormal" patients receiving methohexital		85	63.9	536	+5.64	+.3	+.2	− .97	+ 4.44
Compared to:	10								
"Abnormal" patients receiving thiopental		86	62.9	835.6	+3.16	+.1	+.1	− .92	+ 2.1
"Normal" and "abnormal" patients receiving methohexital		116.4	64.8	614.3	+1.61	+.14	+.14	− .71	+ .41
Compared to:	7								
"Normal" and "abnormal" patients receiving thiamylal		117.9	66.5	1085.7	+3.69	+ 14	0	−1.58	+ 6.49

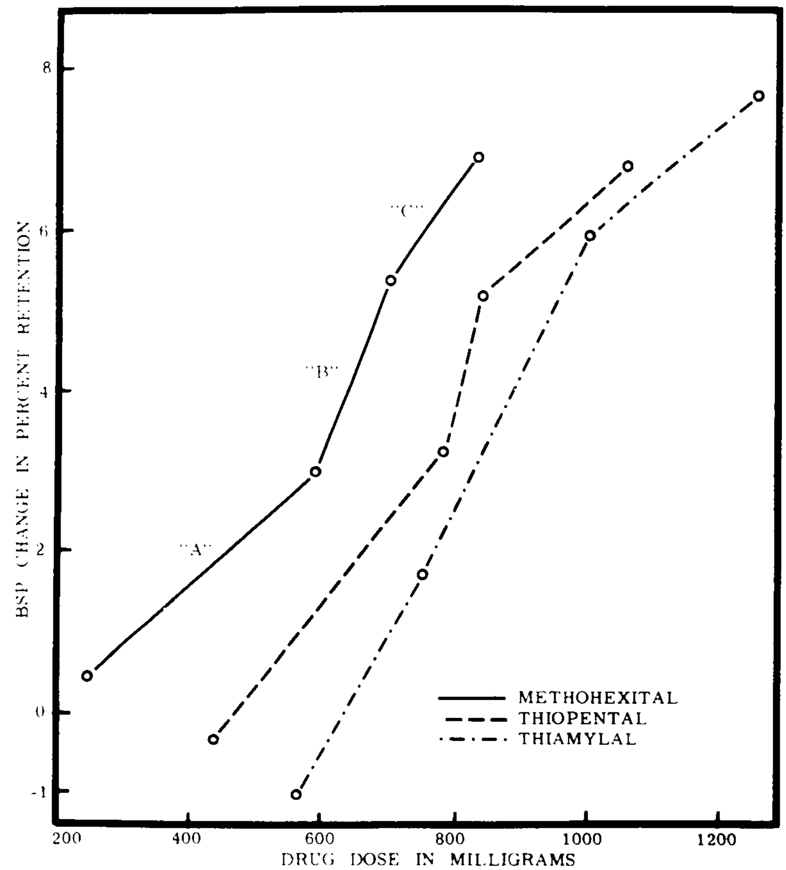

FIG. 1. Correlation of change in BSP retention with drug dosage. Change in BSP as determined for all patients.

analysis. The primary factor to be considered at this point was the relationship between these changes and the average dosage of barbiturate. When similar groups receiving the same drug were compared, the average BSP and SGO-T change was greater in that group receiving the larger dosage. Although the differences in the average dosage were great when groups receiving methohexital were compared to groups receiving thiopental or thiamylal, BSP and SGO-T changes were not in proportion to this difference.

A more detailed correlation between the three barbiturates was made by plotting the effect of increasing total dosage of drug on the preoperative-to-postoperative change in tests (figs. 1 and 2). This correlation was also made between normal and abnormal patients receiving methohexital (figs. 3 and 4). (Work of others suggested that liver test changes were influenced by the type and location of the surgical procedure.[21, 22]) This correlation was also carried out only for those patients having breast or thyroid operations.

Patients receiving the same drug were arranged in order of increasing total dosage and were assembled in small groups so that the increase in total dosage range was 50 mg. to 100 mg. between each group. The amount of change in the preoperative-to-postoperative test results was calculated for each small dosage group. This average change was then plotted against the dosage increment.

All three compounds exhibit a direct relationship between dosage and change in BSP. A given change in BSP occurred over a dosage range which was lowest for methohexital and greatest for thiamylal. When those patients having only breast or thyroid operations were compared, the relation between methohexital and thiopental was the same as that shown in figure 1. For thiamylal, there was an insufficient number of patients to make a comparison. For all the drugs, the graphs were roughly parallel and indicated similar rates of change in BSP with drug dosage but at different total drug-dose levels.

For each barbiturate, the curves in figure 1 resolved themselves naturally into three segments. These segments were designated "A," "B," and "C." Segment "A" covered the low dose range and "B" and "C" the medium and high ranges, respectively. As shown in table 2, the slope of each segment tended to show a certain amount of agreement when comparison was made between the drugs. This was particularly true when only those patients having breast or thyroid operations were considered. Furthermore, rate of change in BSP showed little difference for patients having breast or thyroid operations when compared to those having all types of surgical procedures.

The total dosages of thiopental or thiamylal necessary to produce the same change in tests as methohexital were derived from these curves. The differences in total dosage necessary to produce this change in BSP were expressed as ratios with the methohexital dosage as the denominator. These dosage ratios are shown in table 2. Over segment "A," it required 1.72 times more thiopental and 2.30 times more thiamylal than methohexital to produce the same degree of change in BSP. The average dosage ratio for segment "B" closely agreed with that of segment "C" for thiopental or thiamylal. Dosage ratios for thiopental and thiamylal in these ranges were not as great as in the lower dose range. The dosage ratios of thiopental for patients undergoing breast or thyroid operations were almost identical to the dosage ratios of thiopental for all patients.

The effect of increasing doses of the three barbiturates on the change in the SGO-T is

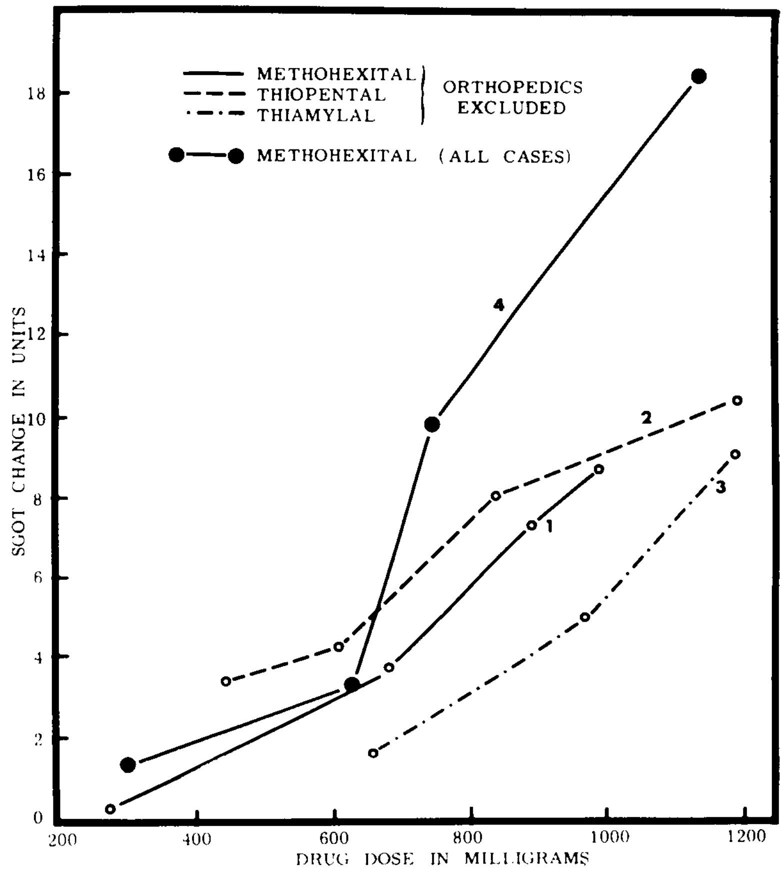

FIG. 2. Correlation of change in SGO-T with drug dosage.

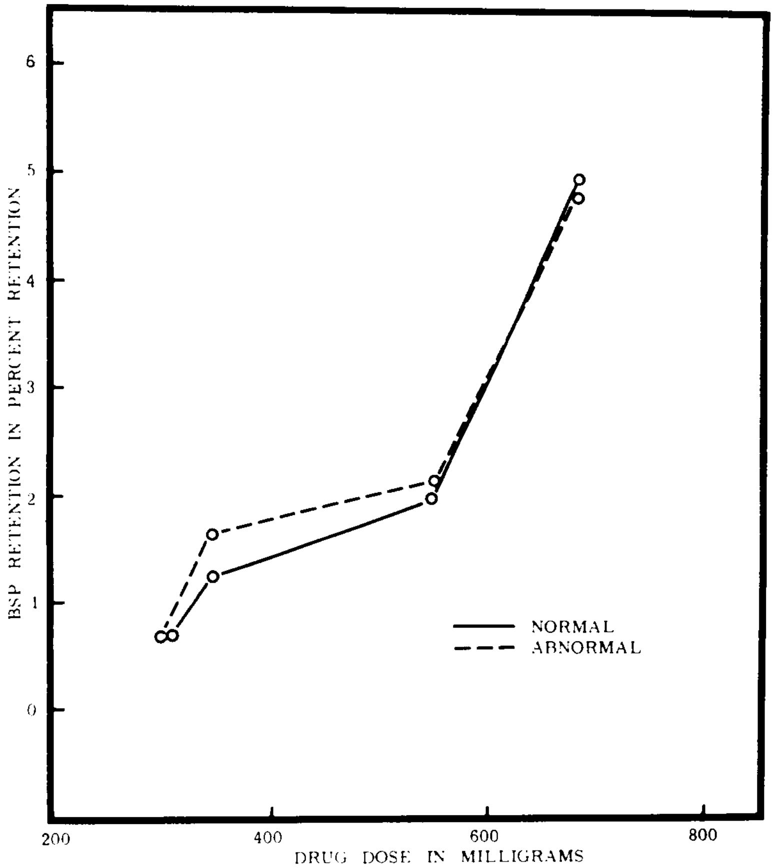

FIG. 3. Comparative change in BSP retention with dosage of methohexital between "normal" and "abnormal" patients.

presented in figure 2. Curves 1, 2, and 3 were derived from all patients with the exception of those who had orthopedic surgery. Curve 4 included patients who had orthopedic surgery. Thiamylal (curve 3) produced the lowest rate of increase of SGO-T with respect to dosage and thiopental (curve 2) the greatest increase. When the SGO-T changes of

TABLE 2. Dosage Ratios for Equal BSP Retention and Comparison of Rate of Change

Drug	Slope Segment A	Dose Ratio*	Slope Segment B	Dose Ratio*	Slope Segment C	Dose Ratio*
Using Patients Having All Types of Surgery						
Methohexital	.007	1	.023	1	.010	1
Thiopental	.010	1.72	.031	1.27	.008	1.27
Thiamylal	.015	2.30	.017	1.40	.006	1.36
Using Patients Having Only Breast or Thyroid Surgery						
Methohexital	.009	1	.019	1	.012	1
Thiopental	.01	1.73	.02	1.21	.013	1.21

* For equal change in BSP retention.

the patients undergoing orthopedic surgery were added to curve 1, methohexital produced the greatest change per dosage.

One-third of the patients receiving methohexital had orthopedic surgical procedures. Those patients accounted for 40 to 78 per cent of the change in the SGO-T at given dosage levels. Because of this proportionately larger number of patients and the presumed effect of muscular damage on the change in SGO-T, the orthopedic patients were not included in comparing dose response curves for SGO-T.

In figure 2, curves 1, 2, and 3 assumed a parallel attitude indicating similar rates of change. Thiopental produced the greater change in SGO-T at a given total dosage level than methohexital, indicating a dosage ratio less than 1.0. Thiamylal produced a lesser change than methohexital over the middle and lower dose ranges. One dosage ratio was calculated for thiamylal at the greatest total dosage difference between methohexital and thiamylal. This ratio was 1.31.

In figures 3 and 4, the BSP and SGO-T change with dose of methohexital for normal and abnormal patients are plotted. These curves indicate no apparent difference in amount of change for abnormal compared to normal patients.

Duration of Anesthesia

Anoxia and hypotension can be major contributors to the changes in liver function tests. The probability of an anoxic or hypotensive episode would be greater as duration of anesthesia increases. To test this, patients were arranged in order of increasing total duration of anesthesia. These patients were grouped so that the increasing total anesthesia time was 15 minutes between each group. The average change in liver function tests was

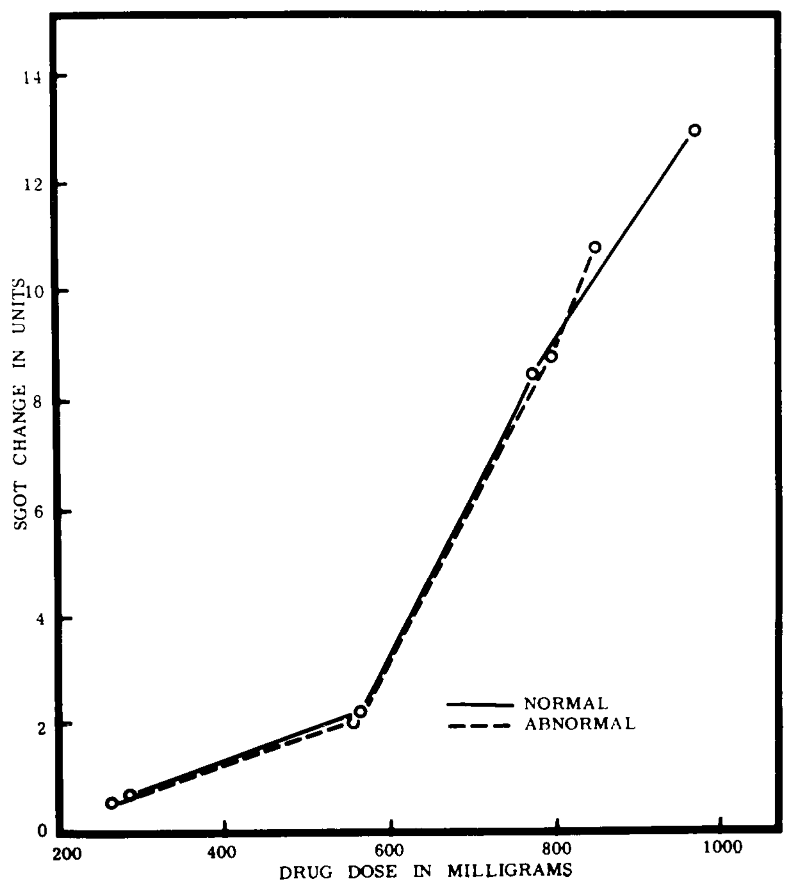

FIG. 4. Comparative change in SGO-T with dose of methohexital between "normal" and "abnormal" patients.

TABLE 3. Dosage Ratios for Equal Anesthesia

Anesthesia Time in Minutes	Thiopental/ Methohexital	Thiamylal/ Methohexital
Induction	2.46	2.37
15	2.58	1.99
30	2.40	2.07
45	2.21	1.94
60	2.02	1.88
75	1.87	1.83
90	1.74	1.79
105	1.66	1.79
120	1.60	1.78
135	1.59	1.72
150	1.56	–

determined for each group. Except in one observation, no correlation with duration was found for any of the tests. It was found that the change in BSP and SGO-T was slightly above the mean at the longest duration of anesthesia (after two and one-half hours). However, because of duration of anesthesia, these patients received a dosage larger than the mean total dosage. The converse was true for the first 30 minutes of anesthesia.

DOSE TO MAINTAIN EQUAL ANESTHESIA

The dose of drug in milligrams/kilogram/minute required to maintain anesthesia was determined after the method of Dundee.[23] From these determinations, the total dosage of thiopental or thiamylal at a given length of anesthesia was divided by the total dosage of methohexital at the same length of anesthesia. The ratios of dosages at specific time intervals between methohexital and thiopental or thiamylal are expressed in table 3. The time intervals were the induction period, and then at 15-minute periods thereafter.

The dosage ratios for thiamylal were less than those for thiopental up to 75 minutes duration of anesthesia, after which they became larger. Less methohexital was required for anesthesia over the entire period of observations than was required for thiopental or thiamylal.

COMPARISON OF DOSAGE RATIOS

The data indicated that on an equal weight-of-drug basis methohexital produced more change in the BSP than the other two drugs. However, a much larger dosage of thiamylal or thiopental was necessary to maintain anesthesia, and the total change in BSP was actually greater with these two compounds. In table 4 a comparison is made between drug dosage ratios necessary for equal BSP changes and equal anesthesia. The dose of methohexital where these comparisons were made is indicated.

The method of determining dosage ratios necessary to produce equal change in BSP was described previously. From the methohexital dose-response curve, the points of inflection and termination were found (fig. 1). The patients representing these points were considered individually. From table 3, the dosage ratio for thiopental or thiamylal for theoretical equivalent anesthesia was determined for each patient. Then the average dosage ratio was calculated from the individual dosage ratios at each point. Except for the low dosage range, the required dosage of thiopental and thiamylal for equivalent anesthesia was approximately 1¾ and 1⅘ times the methohexital dosage, respectively. This is in contrast to 1¼ and 1⅖ times the methohexital dosage for equal BSP change.

Similarly, it may be shown that on an equivalent anesthesia basis methohexital produced less change in SGO-T than thiopental or thiamylal. Specifically, thiopental produced a greater change in SGO-T even on an equal weight basis. If the dosage necessary to maintain the equal anesthesia of methohexital was added, thiopental would produce even a

TABLE 4. Comparison of Drug Dosage Ratios for Equal BSP Change and Equal Anesthesia

Dose Level of Methohexital in Milligrams from Figure 1	Thiopental: Number of Times Methohexital Dose to Give Equal: BSP Change	Thiopental: Number of Times Methohexital Dose to Give Equal: Anesthesia	Thiamylal: Number of Times Methohexital Dose to Give Equal: BSP Change	Thiamylal: Number of Times Methohexital Dose to Give Equal: Anesthesia
236	2.16	2.08	2.80	1.9
588	1.28	1.71	1.4	1.79
695	1.26	1.72	1.4	1.79
834	1.28	1.73	1.38	1.82

Note: The probability that the observed difference in ratios between BSP change and anesthesia will not occur is $P < .001$ for thiopental and $P < .05$ for thiamylal.

greater change in SGO-T. On an equal weight basis thiamylal did not produce as much change in SGO-T as methohexital. The largest dosage ratio for equal change in SGO-T was 1.31, but dosage ratios necessary to maintain equal anesthesia were well above this (table 3). On an equivalent anesthesia basis thiamylal would produce a greater change in SGO-T than methohexital.

The results of the general gross comparison between the three barbiturates form the basis of two conclusions: (1) All three barbiturates affected liver function in the same manner. (2) Patients with mild to moderate liver impairment were affected no more than normal patients.

The initial detailed comparison established a relationship between the type of liver function test that underwent significant change and the three barbiturates. Within the dosage range of this study, the cephalin-cholesterol flocculation and thymol turbidity as well as the alkaline phosphatase and inorganic phosphate were useless in determination of any difference between these barbiturates. This conclusion supports that of Tagnon.[21] As Tagnon found, there were significant changes in the BSP; and as expected from Aperson's study,[22] there were significant changes in the SGO-T. In this study, these changes were directly related to the amount of barbiturate.

Evaluating the effect of other possible causes for changes in liver function tests led to three conclusions: (1) Since there was no correlation between duration of anesthesia and change in liver function tests, anoxia and hypotension were not major contributors to the test changes found in this study. (2) Changes in BSP were independent of the type of surgical procedure. Patients having orthopedic surgery showed a greater increase in SGO-T, which is not unusual as these patients had relatively greater muscle damage.[22] Type of surgical procedure had no effect on the change in cephalin-cholesterol flocculation or thymol turbidity. (3) BSP and SGO-T changed at the same rate and amount per dosage in both "normal" and "abnormal" patients. Therefore, methohexital is no more toxic to patients with mild to moderate liver depression than patients with normal liver function.

Change in BSP and SGO-T (excluding patients having orthopedic surgery) was directly related to the weight of barbiturate, and increased dosage ratios were found between methohexital and the other two drugs for equal change in BSP. For equal change in SGO-T, dosage ratios were decreased between methohexital and thiopental but increased between methohexital and thiamylal. Therefore, a given amount of methohexital depresses or injures the liver more than the same amount of thiopental or thiamylal, as measured by the BSP. As measured by the SGO-T, methohexital depresses the liver less than thiopental but more than thiamylal.

As found in this study and in others, the amount of methohexital required for anesthesia is much less than that of thiopental or thiamylal. The comparison of dosage ratios based on equal change in BSP and SGO-T and dosage ratios based on equal anesthesia between the three barbiturates leads to the final conclusion: *Methohexital produces less depression of liver function than thiopental or thiamylal on the basis of equal anesthesia.*

Summary

A comparative study of the effect on liver function tests by three ultrashort-acting intravenous barbiturates was made. In general, all three drugs changed liver function in the same manner. On a weight of drug basis methohexital produces more depression of liver function than thiopental or thiamylal. However, based on amounts of drug required for anesthesia, methohexital produces less depression of liver function. In patients with pre-existing liver-function depression, methohexital did not increase this depression more than in patients with normal liver function.

This study was supported by the Eli Lilly Company who also supplied the methohexital (Brevital). The authors acknowledge the aid of Mr. L. Harkness, Ford Motor Company, for statistical approach to and evaluation of data.

References

1. Stoelting, V. K.: Use of a new intravenous oxygen barbiturate 25398 for intravenous anesthesia, Anesth. Analg. **36**: 49, 1957.
2. Gruber, C. M., Stoelting, V. K., Fornay, R. B., White, P., and DeMayer, M.: Comparison of an ultrashort acting barbiturate (22451)

with thiobarbiturates during anesthesia, ANESTHESIOLOGY **18**: 50, 1957.
3. Wyant, C. M., Dobkin, A. B., and Aashein, C. M.: Comparison of seven anesthetic agents in man, Brit. J. Anesth. **29**: 194, 1957.
4. Egbert, L. D., Oech, S. R., and Eckenhoff, J. E.: Comparison of the recovery from methohexital and thiopental anesthesia in man, Surg., Gynec. Obstet. **109**: 427, 1959.
5. Weyl, R., Unal, B., and Alper, Y.: Clinical evaluation of a new ultrashort acting oxygen barbiturate for intravenous anesthesia, Surg., Gynec. Obstet. **107**: 588, 1958.
6. Taylor, C., and Stoelting, V. K.: Methohexital sodium—A new ultrashort acting barbiturate, ANESTHESIOLOGY **21**: 29, 1960.
7. Gibson, W. R., Swanson, E. E., and Doran, W. J.: Pharmacology of a short-acting nonsulphur barbituric acid derivative, Proc. Soc. Exp. Biol. Med. **89**: 292, 1955.
8. Mark, L. C., Brand, L., Dayton, P., Blaber, P., and Pepper, E. M.: Behavior of methohexital in man, Fed. Amer. Soc. Exp. Biol. **19**: 274, 1960.
9. Richards, R. K., and Taylor, J. D.: Some factors influencing distribution, metabolism, and action of barbiturates: a review, ANESTHESIOLOGY **17**: 414, 1956.
10. Walton, C. H., Saldamando, J., and Egner, W. M.: The effect of intravenous Pentothal sodium with or without inhalation of oxygen on liver function, ANESTHESIOLOGY **12**: 67, 1951.
11. Shideman, F. E., Kelly, A. R., Lee, L. E., Lowell, V. E., and Adams, B. J.: Role of liver in detoxification of thiopental (Pentothal) in man, ANESTHESIOLOGY **10**: 42, 1949.
12. Meyers, F. H., and Peoples, D.: The positive role of the liver in the rapid metabolism of thiopental, ANESTHESIOLOGY **15**: 146, 1954.
13. Haselhuhn, D. H.: The use of Pentothal in the presence of severe hepatic disease, Anesth. Analg. **36**: 73, 1957.
14. Walton, C. H., Uhl, J. W., Egner, W. M., and Livingstone, H. M.: Use of thiopental sodium intravenously in presence of hepatic damage, Arch. Surg. **60**: 986, 1950.
15. Seligson, D., Marino, J., and Dodson, E.: The determination of sulfobromophthalein in serum, Clin. Chem. **3**: 638, 1957; Seligson, D., and Marino, J.: Sulfobromophthalein (BSP) in serum, *In:* Standard Methods of Clinical Chemistry, Seligson, D., Editor-in-Chief. New York, Academic Press, Inc., 1958, vol. II, pp. 186–191.
16. Kaser, M. M., and Baker, J.: Standard Methods of Clinical Chemistry, Vol. II, pp. 122–129. (But using color development reagent as described by Gomori, G.: J. Lab. Clin. Med. **27**: 955, 1941–1942.)
17. Gomori, G.: J. Lab. Clin. Med. **27**: 955, 1941–1942.
18. Kingsley, G. R., and Getchell, G.: Standard Methods of Clinical Chemistry, Mariam, R., Editor-in-Chief. New York, Academic Press, Inc., 1953, Vol. I, pp. 113–117. (Method of Shank, R. E., and Hoagland, C. L.: J. Biol. Chem. **162**, 133, 1946.)
19. Reitman, S., and Frankel, S.: Amer. J. Clin. Path. **28**: 56, 1957.
20. Knowlton, M.: Standard Methods of Clinical Chemistry. New York, Academic Press, Inc., 1958, Vol. II, pp. 12–21.
21. Tagnon, H. J., Robbins, G. F., and Nichols, M. P.: The effect of surgical operations on the Bromsulfalein-retention test, New Engl. J. Med. **238**: 556, 1948.
22. Aperson, D., and Judge, R. D.: Effect of operation on serum transaminase levels, Arch. Surg. **77**: 892, 1958.
23. Dundee, J. W.: Observations on the dosage and cumulative action of thiopentone, ANESTHESIA **10**: 139, 1955.