Studies with Thiohexital, an Anesthetic Barbiturate Metabolized with Unusual Rapidity in Man

Lester C. Mark, M.D., James M. Perel, Ph.D.,† Leonard Brand, M.D.,‡ Peter G. Dayton, Sc.D.§*

Thiohexital, a des-methyl-thio analog of methohexital, has been found to be the most rapidly metabolized intravenous barbiturate yet studied in man. It is more highly bound to plasma proteins than are thiopental and methohexital. The uptake by human adipose tissue, studied *in vivo* by means of serial biopsies, was considerably less than the uptake of thiopental. An analysis which correlates clinical features of the drug with physicochemical and metabolic factors is presented. It appears that a more rational approach to drug design based on these considerations would lead to a superior anesthetic barbiturate.

AN IDEAL intravenous anesthetic agent should pass quickly into the brain and produce an adequate clinical effect. Upon termination of administration, the drug should disappear rapidly from the brain to permit early awakening. This should be coupled with and aided by rapid biotransformation, in turn unhindered by extensive accumulation in body fat depots.

A problem in the search for such a drug has been the relatively slow metabolism in man encountered with each new compound examined. For example, the rates of metabolism of methitural (Neraval) (20 per cent per hour)[1] and methohexital (Brevital) (15–19 per cent per hour)[2, 2a] are in the same range as, and only slightly faster than, that of thiopental (Pentothal) (15 per cent per hour).[3] Other barbiturates are metabolized even more slowly.[4] Thus, up to the present time, the figure of 20 per cent per hour has seemingly represented a ceiling for this parameter in the barbiturate family of drugs.

Since thiopental is transformed in man at a faster rate than its oxygen analog, pentobarbital (Nembutal),[5] it appeared reasonable that substitution of a sulfur atom in place of the oxygen in position 2 of the metohexital molecule would result in accelerated metabolism. In attempts to accomplish the synthesis, the thio analog of methohexital proved unstable (Chen, K. K., personal communication), but the des-methyl-thio analog (thiohexital, Lilly 22113) (fig. 1) was made available to test the hypothesis.

Preliminary studies in animals were accomplished by Lilly Research Laboratories. Median anesthetic doses of thiohexital, methohexital and thiopental in rats, dogs and cats appear in table 1. In dogs, induction of anesthesia with thiohexital was rapid and smooth and recovery uneventful; in rats, tremors marred both induction and recovery; in cats excitability was common during recovery.

Acute toxicity of thiohexital in rats, expressed as $LD_{50} \pm$ S.E., was produced by 42.0 $\pm$ 1.5 mg/kg body weight. For methohexital and thiopental these figures were 31.0 $\pm$ 2.1 and 37.3 $\pm$ 1.5 mg/kg, respectively. The

* Professor of Anesthesiology, College of Physicians and Surgeons.

† Associate Research Scientist, New York Research Service, Goldwater Memorial Hospital. Present address: Psychiatric Institute, College of Physicians and Surgeons, Columbia University, New York, New York.

‡ Associate Professor of Clinical Anesthesiology, College of Physicians and Surgeons.

§ Research Scientist, New York University Research Service, Goldwater Memorial Hospital. Present address: Departments of Medicine and Pharmacology, Emory University School of Medicine, Atlanta, Georgia.

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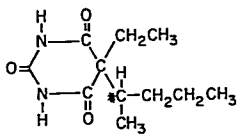
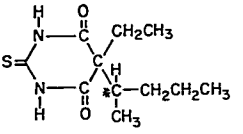
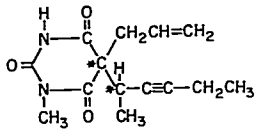


PENTOBARBITAL

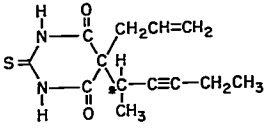


THIOPENTAL

FIG. 1. Structural formulae. Asterisks mark asymmetric carbon atoms.



METHOHEXITAL



THIOHEXITAL

compounds thus appear to have similar therapeutic indices in animals.

These data concern efficacy and lack of unusual toxicity in several animal species. For obvious reasons, they are an essential prelude to, but no substitute for, human studies. The present paper presents evidence that thiohexital is more rapidly metabolized in man than other known barbiturates.*

Methods and Material

The free acid of thiohexital sodium (dl-5-(1-methyl-2-pentynyl)-5-allyl-2-thiobarbituric acid) was prepared by dissolving 1 g of the salt in 18 ml of water and cooling to 0–5° C; upon adjusting to *p*H 5 with 1 *N* acetic acid, the barbituric acid precipitated. The mixture was centrifuged to facilitate collection of the solid by filtration. After washing with water, the material was dissolved in a small amount of ethanol and decolorized with a pinch of charcoal. Upon crystallization from ethanol water, it melted at 132–133° C, confirming purity.

The spectrophotofluorometric method of analysis of thiohexital in plasma is essentially the same as that previously reported for thiopental,[6] except for the following modifications. The organic solvent employed is 1.5 per cent isoamyl alcohol in n-heptane.† Purification of the n-heptane and isoamyl alcohol is carried out in the manner described by Dayton *et al.*[6] The biological sample (up to 3 ml) is introduced into a 60-ml bottle, and 0.5 ml. of 3 *N* HCl and 30 ml solvent are added. The total aqueous volume is held constant at 3.5 ml by adding water when necessary. For analysis of thiohexital in urine, the urine is treated like plasma, except that prior to extraction of the drug into NaOH (Mallinckrodt or Fisher) the organic phase is shaken with an equal volume of *p*H 6.5 citrate (0.1 *M*)—disodium phosphate (0.2 *M*) buffer to reduce "blank." Activation and fluorescence parameters are 308 and 512 mμ, respectively. Another modification is that the shutter of the instrument is kept closed until the last possible moment to avoid excessive exposure of the solution to ultraviolet radiation. The spectrophotofluorometric method of analysis generally yields more than 90 per cent recovery with 5 to 10 μg. The limits of the method (0.1–0.3 mg/l) and the low "blanks" encountered (average reagent blank 0.1 μg, average plasma blank 0.3 μg for 1–3 ml plasma) are the same as for thiopental.

* Most of the research antedated present regulations of The Food and Drug Administration and guidelines of The National Institutes of Health governing investigation of new drugs in man. In the last few studies the guidelines were carefully followed, with little change in the original protocols.

† N-heptane (99 mole per cent minimum) was bought in drums from Phillips Petroleum Corp., Bouger, Texas.

Urine was examined for metabolites by extraction under acidic conditions into dichloromethane. The solvent was divided into two portions, of which one was extracted with NaOH for direct analysis, while the other was dried with Na_2SO_4, evaporated and its remainder transferred to a thin-layer plate with ethanol for chromatographic separation.

Specificity of the plasma method was examined by a quantitative thin-layer chromatographic method as follows: each of three subjects was given thiohexital sodium, 900 mg, intravenously for a period of eight to 12 minutes. Samples of venous blood were withdrawn before administration of drug and at intervals from a half hour to five hours after the beginning of the injection. Plasma was extracted in the presence of HCl as described, except that dichloromethane was used as the solvent. The conditions for thin-layer chromatography on silica gel G were essentially the same as those described for thiopental.[6] In this system, the R_f ‡ of the drug was 0.57 ± 0.05. Areas containing drug were scraped and the gel extracted with dichloromethane; the drug was then re-extracted with 2.5 *N* NaOH. The results of analysis by the n-heptane-isoamyl and quantitative thin-layer methods in parallel were the same, within experimental error. Specificity of the method for urine was tested by the method of partition coefficients[7] in a system using Clark and Lubs buffers (*p*H 7.2–8.4) and isoamyl alcohol 1.5 per cent in n-heptane.

The partition coefficient of thiohexital between peanut oil and *p*H 7.4 Sörensen buffer was determined as described by Perel *et al.*,[8] in a modification of the method of Mark *et al.*[9] The pK_a was measured spectrophotometrically[10] in water at room temperature, by measuring absorbance at 290 mμ. The dissociation constant was also obtained potentiometrically at room temperature by dissolving 26.5 mg of thiohexital in 15 ml of 90 per cent ethanol and titrating with 0.02 *N* NaOH.

The amount of drug bound to human plasma was determined as previously described[8] by placing 5-ml aliquots of plasma in cellophane bags, adding 1 ml of *p*H 7.4 *M*/15 Sörensen buffer to control bags and the same amount of buffer containing drug to other bags. Each bag was placed in a tube containing 17 ml of buffer and incubated at 37° C.

The rate of biotransformation was studied in ten subjects undergoing elective surgery after receiving thiohexital sodium in 1 per cent (occasionally, 2.5 per cent) solution in doses of 900 to 1000 mg intravenously, within eight to 15 minutes. Anesthesia was supplemented with nitrous oxide. Blood samples for determination of drug concentrations in plasma were withdrawn at intervals as late as seven hours from the beginning of injection.

Urinary excretion of thiohexital and its metabolites was studied in three subjects who received thiohexital sodium, 900 mg intravenously, under similar conditions; urine was collected for 24 hours for isolation studies of transformation products.

The amount of drug localized in fat was investigated in four subjects undergoing abdominal operations. They received thiohexital sodium, 900 to 1000 mg intravenously, supplemented with light cyclopropane anesthesia and muscle relaxant drugs as needed. Samples of subcutaneous and omental adipose tissue and

‡ R_f is defined as the ratio $\frac{\text{distance travelled by the compound}}{\text{distance travelled by the solvent front}}$ on the thin-layer plate.

TABLE 1. Median Anesthetic Doses of Various Barbiturates*

Species	Thiopental		Thiohexital		Methohexital	
	Dose (mg/kg)	Total Duration (min)	Dose (mg/kg)	Total Duration (min)	Dose (mg/kg)	Total Duration (min)
Rat	29.0 ± 1.5	186	23.7 ± 0.9	68	14.2 ± 0.9	22
Dog	16.0 ± 1.0	142	10.8 ± 1.0	38	9.7 ± 0.9	29
Cat	10.4 ± 0.9	58	6.5 ± 0.4	211	5.8 ± 0.5	39

* These data are reproduced with the permission of Dr. D. F. Stone, Eli Lilly and Company. All drugs were administered intravenously.

blood were obtained at appropriate intervals during the surgical procedure.

Recovery from thiohexital–nitrous oxide anesthesia for minor gynecological operations (either cervical dilatation and uterine curettage or ligation of fallopian tubes) was studied in healthy women. Preanesthetic medication consisted of secobarbital (Seconal), 50–150 mg, and scopolamine or atropine, 0.4–0.5 mg. (Three subjects also received meperidine (Demerol), 50–75 mg, one subject, atropine, 0.75 mg. alone). Thiohexital was administered intravenously as required in conjunction with nitrous oxide anesthesia (nitrous oxide 6, oxygen 2, l/min). Total doses of thiohexital ranged from 140 to 330 mg; the time from start of anesthesia to end of operation varied from 11 to 46 minutes. Waking times were noted in terms of each subject's ability to (a) open eyes on command and (b) report her telephone number. For purposes of crude comparison, similar observations of five other patients who received thiopental and three who received methohexital were made.

Results

Specificity studies of the analytic method employing a thin-layer chromatographic technique resulted in more than 95 per cent specificity for plasma; for urine, specificity was at least 90 per cent, based upon the method of partition coefficients.

Several chemical properties of thiohexital were determined. The pK_a is 7.25 ± 0.05 in water, but 9.6 ± 0.05 in ethanol; 88 to 90 per cent was bound to human plasma proteins at an equilibrium concentration of 10 mg/l inside the dialysis bag. In parallel experiments with thiopental, using aliquots of the same plasma, 79 to 81 per cent of the drug was bound. Maximal ultraviolet absorption of the compound in 2.4 *N* NaOH occurs at 308 mμ; in 1 *N* HCl the maximum occurs at 290 mμ, with a secondary peak at 240 mμ. The partition coefficient between peanut oil and buffer is 85, compared with 65 and 89 for methohexital and thiopental, respectively.[2]

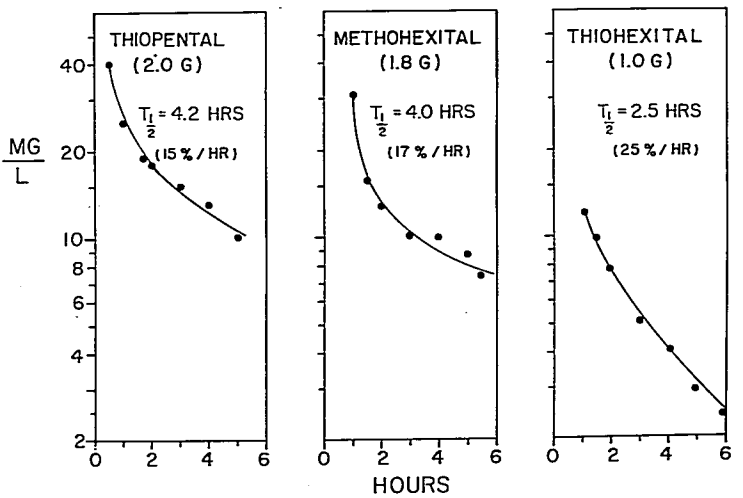


FIG. 2. Typical results. Decline of plasma levels of drugs in different human subjects.[2]

Studies in Man

Rate of Biotransformation. Figure 2 shows typical plasma decay curves for thiohexital, methohexital and thiopental. Thiohexital was metabolized at a rate of 25 per cent per hour, compared with 15 and 17 per cent per hour for thiopental and methohexital, respectively.

Following intravenous administration, plasma levels of thiohexital declined rapidly for an hour to two and a half hours, then fell more slowly. This point of inflection did not occur in one unusual subject (O.C.), in whom metabolism of thiohexital was extremely rapid. The results of plasma decay experiments with thiohexital appear in table 2. In each case, rate of metabolism was calculated from rate of plasma level decline, after allowing sufficient time (one and a half to two hours) for establishment of diffusion equilibrium of drug distribution between plasma and body tissues. (On statistical grounds, the data from subject O.C. were excluded from the averaging of half-lives.)

After this time, of course, the assumption that half-life approximates rate of biotransformation is valid only if excretion is negligible. In the case of thiohexital almost all of the drug undergoes metabolic alteration in the body; less than 1.5 per cent was excreted in the urine during the 24 hours following administration of 900 mg.

Extraction of the urine with dichloromethane, a more polar solvent than heptane and isoamyl alcohol, 1.5 per cent, disclosed the presence of metabolites corresponding to about 5 per cent of the parent thiohexital, assuming these metabolites to have the same fluorescence. Additional evidence for the formation of at least two metabolites has been obtained with the thin-layer chromatographic technique, R_f values for these metabolites in two different solvent systems are listed in table 3. Upon incubation of the urine with β-glucuronidase, there was a small increase of material chromatographically similar to the two metabolites.

Localization in Adipose Tissue. The results of experiments dealing with the uptake of drug by adipose tissue are given in table 4. Thiohexital is intermediate between methohexital and thiopental in rate and extent of uptake. In part, this can be explained by the slightly lower lipid solubility of methohexital.

In five of six experiments with methohexital, omental fat:plasma ratios stayed below 3.3, but in one exceptional case the ratio reached 6.4. At three hours the ratio for thiohexital ranged from 2.2 to 5.8 with omental fat and from 3.9 to 6.8 with subcutaneous fat, whereas for thiopental at only two to two and a half hours it had reached 8.4 to 12.2 with omental and 3.8 to 7.4 with subcutaneous fat (Mark *et al.*, unpublished results).

Recovery from Thiohexital–Nitrous Oxide Anesthesia. After termination of thiohexital–nitrous oxide anesthesia, subjects could open their eyes on command in two to eight minutes and report telephone numbers in two to 20 minutes (table 5). Comparable times were six to 20 minutes and nine to 34 minutes, respectively, with thiopental, and seven to ten

Table 2. Half-life of Thiohexital in Human Subjects*

Subject	Sex	Half-life (hours)	Per Cent Metabolized per Hour
M.G.	F	1.7	35
S.A.	M	1.8	31
P.D.	F	2.3	28
A.A.	F	2.4	26
R.C.	F	2.4	26
R.D.	F	2.5	25
I.W.	M	4.0	17
B.B.	F	4.0	17
C.L.	F	4.0	17
Average†		2.8±0.8	25±6
O.C.	F	1.0	50

* Dose 1 g of sodium salt intravenously.
† Averages do not include subject O.C.

Table 3. Chromatographic Properties of Thiohexital and Metabolites

Compound	R_f	
	Benzene–glacial acetic acid 7:1	Benzene–glacial acetic acid 4:1
Metabolite A	0.19±0.05	0.12±0.05
Metabolite B	0.30±0.05	0.38±0.05
Thiohexital	0.45±0.05	0.75±0.05

TABLE 4. Uptake of Thiohexital by Adipose Tissue

Subject	Dose* (g)	Time† (min)	Plasma Concentration (mg/l)	Adipose Tissue: Plasma Ratio	
				Omental	Subcutaneous
1	1.0	61	9.5	2.8	1.3
		190	4.2	4.2	3.9
2	1.0	190	3.9	2.2	5.1
3	0.9	29	16	1.1	0.8
		64	7.4	2.8	1.8
		85	5.5	4.7	3.3
		99	5.1	—	3.1
4	0.9	131	2.4		5.9
		190	1.8	5.8	6.8
		221	1.8	4.5	5.8
		277	1.5	6.9	6.7

* As sodium salt.
† From beginning of injection.

and 10 to 31 minutes with methohexital. Side effects of twitching, tremors or hiccough noted during anesthesia in some subjects were suppressed readily by further administration of thiohexital.

Discussion

The finding that biotransformation of thiohexital proceeds in man at an average rate of 25 per cent per hour proves that the 20 per cent per hour "ceiling" for metabolism of barbiturates[4] can be overcome. Thus, thiohexital approaches more nearly the requirements of an ideal intravenous anesthetic agent. Examination of the pharmacodynamic factors involved reveals some of the reasons for arriving at this conclusion.

Immediately after intravenous administration of a lipid-soluble barbiturate such as thiopental or thiohexital, plasma levels decline rapidly. This is due primarily to redistribution into tissues,[3, 11, 12] although biotransformation is taking place simultaneously. In the case of thiopental in man, however, metabolism occurs too slowly to play a major role in early recovery. Thus, after thiopental, 300 mg intravenously, durations of sleep in two small groups of subjects were identical (two to 19 minutes in the severely impaired, four to 15 minutes in the mildly impaired group), despite the absence of significant drug metabolism in the first group.[13] From the evidence of plasma decay curves, hepatic extraction of thiohexital is much greater than that of thiopental. This could contribute importantly to both the earlier awakening and the shorter period of drowsiness following return to consciousness after the former drug. Of course, even after diffusion equilibrium has been achieved, resulting in a relatively small per cent of the dose of barbiturate perfusing the liver per unit time, the more rapid metabolism of thiohexital would continue to contribute usefully to the lessening of pharmacologic effects.

Beyond the comparison with thiopental, the clinical impression was gained that subjects receiving thiohexital awaken more promptly and are more alert than those receiving comparable doses of methohexital. The greater binding of thiohexital to plasma proteins could contribute to this difference. Transfer into areas of interest, such as adipose tissue, brain and liver, is dependent on a variety of physicochemical factors, including lipid solubility and protein binding.[6] The figures of 89, 85 and 65 for the lipid solubilities of thiopental, thiohexital and methohexital, respectively, while dissimilar, do not differ importantly.[2] Protein binding is another story. Whereas 75–80 per cent of either thiopental or methohexital is bound to human plasma protein, 88 per cent of thiohexital is bound in comparable conditions. This seemingly small discrepancy may be crucial: it indicates that the free thiohexital concentration (12 per cent) is about half that (20–25 per cent) of the other barbiturates. At steady-state conditions this results in lower values for adipose tissue:plasma and other tissue:plasma concentration ratios of thiohexital, contributing to its lesser accumulation in fat compared with thiopental.[6] The net effect is to present proportionately higher plasma concentrations of thiohexital to the liver for biotransformation.

Motor side effects of hiccoughs and twitching of extremities were observed following thiohexital in about 35 to 40 per cent of cases where such observations were feasible. This phenomenon is highly reminiscent of findings in the early clinical use of compound 22451, a mixture of four stereoisomers.[14] An investi-

TABLE 5. Recovery Periods After Various Barbiturates

Barbiturate	Subject*	Weight (kg)	Premedication† (mg)	Dose‡ (mg)	Time§ (min)	Open Eyes (min)	Waking Time¶ (min)
Thiohexital	1	101	B 150 S 0.5	200	17	2	7
	2	51	B 100 S 0.5	180	22	8	20
	3	70	A 0.75	330	46	2	2
	4	63	B 125 S 0.4	180	30	5	8
	5	67	B 100 A 0.5	300	32	5	5
	6	54	B 100 M 75 S 0.5	140	45	5	15
	7	54	B 100 M 50 A 0.5	150	15	6	7
	8	66	B 100 M 50 A 0.5	250	11	7	7
	9	57	B 100 S 0.4	195	15	7	7
	10	63	B 100 S 0.4	280	26	3	3
Thiopental	11	94	B 125 M 50 A 0.5	425	32	6	9
	12	45	B 100 S 0.4	250	19	14	34
	13	50	B 100 S 0.5	400	16	20	24
	14	100	B 150 S 0.5	325	42	15	21
	15	48	B 100 S 0.5	325	24	16	26
Methohexital	21	78	B 100 S 0.5	150	15	7	10
	22	90	B 50 A 0.5	260	39	8	13
	23	58	B 100 A 0.5	460	57	10	31

* All subjects except subject 3 underwent dilatation and curettage. Subject 3 coughed once and showed one facial twitch, subject 5 coughed once and subject 9 showed one forearm twitch.

† A = atropine; B = secobarbital; M = meperidine; S = scopolamine.

‡ Sodium salt.

§ From beginning of injection of thiohexital to end of operation.

¶ From end of operation, ability to give phone number.

gation of the pharmacology of each isomer[15] made it possible to select a racemic mixture (now used clinically as methohexital) producing the lowest incidence of side effects[16] while retaining therapeutic activity. Similar individual study of each of the two stereoisomers of thiohexital (fig. 1) might conceivably allow separation of undesirable effects from the features of therapeutic activity and rapid metabolism. The rate of biotransformation of one of

the isomers might even be faster than that of dl-thiohexital.

There is no doubt that a compound that has the same properties in man as thiohexital, with fewer side effects, would be extremely useful in clinical practice.

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