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Thiamylal: Review of the Literature and Report of a Suicide

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ABSTRACT: A 28-year-old white male medical student was found hanging by the neck from the bathroom closet of a hotel room. An intravenous infusion line leading from a bottle of thiamylal sodium (an ultrashort-acting barbiturate) was inserted into the antecubital vein of the left arm. Blood was analyzed for alcohol and other volatiles and for acidic, basic, and neutral drugs. Only thiamylal was detected. Thiamylal was quantified by high-performance liquid chromatography with ultraviolet detection, and its presence was confirmed by gas chromatography/mass spectrometry. The tissue distribution of thiamylal was 29 mg/L in blood, 1.4 mg/L in urine, 16 mg/L in bile, 135 mg/kg in liver, 25 mg/kg in kidney, and 0.4 mg in the stomach contents. The uptake and distribution of thiamylal is similar to thiopental. The distribution of the drug in this case was compared to that of other fatalities involving ultrashort-acting barbiturates.

KEYWORDS: pathology and biology, suicide, thiamylal, thiopental, tissue distribution

Thiamylal sodium, sodium-5-allyl-5-(1-methylbutyl) thiobarbiturate (Surital™), is an ultrashort-acting thiobarbiturate which is used as a general anesthetic [*1*]. It is structurally similar to thiopental, differing by substitution at the 5-position on the barbituric acid ring (Fig. 1); thiamylal has an allylic group in this position, whereas thiopental is substituted with an ethyl group. The pKa's for thiamylal and thiopental are 7.5 and 7.6, respectively. Both drugs are slowly metabolized in the liver at a rate of about 10%/h. The primary metabolite is a carboxylic acid derivative, and approximately 10% of the total dose is desulfurated to the oxybarbiturate derivative. A rapid and smooth induction of anesthesia is achieved with 3 to 6 mL of a 2.5% thiamylal solution [*2,3*]. Complications of thiamylal-induced anesthesia have been described as laryngospasm, cyanosis, respiratory depression, bronchospasm, and cardiac arrhythmias [*4,5*]. These complications, especially respiratory depression, may lead to death if mechanical assistance is not available. A review of the literature revealed one report of a clinical anesthetic death involving thiamylal [*6*]. Toxicological analysis was not reported. This report describes a suicide by means of hanging and thiamylal intoxication.

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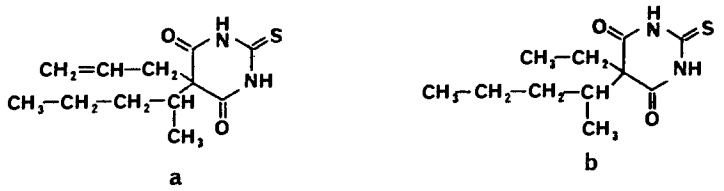

FIG. 1—*Chemical structures of thiamylal* (a) *and thiopental* (b).

Case Report

A 28-year-old white male medical student checked into a motel during the evening. He was last seen alive at 9:30 the following morning. When checkout time had passed, an investigation by motel personnel found the deceased's motel room door locked from the inside. The police were alerted to search the room. At 4:00 p.m. the body was found hanging by the neck with knees bent and toes touching the floor in a bathroom closet with an intravenous (IV) infusion dripping into the left antecubital vein. The IV bottle was labeled Surital™ 10 g and contained approximately 200 mL fluid. In addition, three plastic bags were found with the body. One contained surgical gloves, syringes, and alcohol prep sponges. A second bag contained only a tie and a rubber band, and the third bag contained a sphygmomanometer and a medication vial labeled "Valium 5 mg," which was prescribed for the deceased. Also found with the deceased were hospital chart notes referring to several geriatric patients and a suicide note.

External examination of the body showed a 5 ft 10-in. (178-cm), 178-lb. (80-kg) well-developed white male with multiple Tardieu spots in the skin of the lower extremities. The sclerae and palpebral conjunctivae showed multiple petechial hemorrhages. Examination of the neck described an abraded ligature mark with punctate hemorrhages on the skin. Internal examination showed mild congestion of the lung, renal, and liver parenchyma. The tongue was markedly livid and dry in the anterior portion. All other tissues and organs were unremarkable.

Methods

Materials

Thiamylal sodium was obtained from Parke Davis (Morris Plains, New Jersey) and a 200-mg/L solution in methanol prepared. Phenolphthalein was acquired from Aldrich Chemical Co. (Milwaukee, Wisconsin) and a 1-mg/mL solution in methanol used as the internal standard for quantification by HPLC.

Potassium biphthalate was Fisher A.C.S. grade; 13.1 g were dissolved in 1 L water and the pH was adjusted to make a pH 5 buffer (0.1*M*). Methanol and water were Fisher high-performance liquid chromatography (HPLC) grade, and methylene chloride was pesticide grade. Clin-Elut solid-phase extraction columns were obtained from Analytichem International (Harbor City, California).

Extraction for HPLC Analysis and GC/MSD Confirmation

To 2.0 mL fluid or tissue homogenate (one part tissue to four parts buffer) were added 2 mL pH 5 buffer and 100 μg phenolphthalein. After vortexing for 10 s, the solution was applied to a Clin-Elut column and allowed to adsorb onto the column for 10 min. The columns were then washed three times with 5 mL methylene chloride, and the eluate was collected in a 12-mL conical tube. The extract was evaporated under a stream of air

at 60°C. The dried residue was reconstituted with 200 μL methanol, and 20 μL were injected into the liquid chromatograph. One microlitre of this residue was also injected into the gas chromatography/mass spectrometry (GC/MS) system.

Instrumentation

A model 334 gradient liquid chromatograph (Altex) attached to a model 11-30 to variable-wavelength detector (Hitachi) and a model 3390 integrator (Hewlett-Packard) was used for thiamylal quantification. Thiamylal and phenolphthalein were separated on an ODS 5 μm (4.6 mm inside diameter by 15 cm) column (Altex). The mobile phase was methanol:water (5:1 by volume) with a flow rate of 2.0 mL/min. The wavelength of detection was 290 nm and the detector range 0.05 A full-scale.

A model 5890 GC attached to a series 5970 mass selective detector (MSD) was used to confirm the presence of thiamylal. The *m/z* of greatest abundance was 184, and the mass spectrum of the extracted blood sample was compared with that of the thiamylal standard (Figs. 2 and 3).

Results and Discussion

The blood was tested for volatiles (methanol, ethanol, isopropanol, and acetone) and for acidic, basic, and neutral drugs. Only thiamylal was detected. Subsequently, the liver, kidney, stomach content, bile, and urine were analyzed and quantified. No fat or brain samples were available for analyses.

Thiamylal is similar to thiopental, and the two drugs have been compared by several investigators. Kelly et al. [7] injected dogs intravenously at a dose of 20 mg/kg using a 4% solution of either thiamylal or thiopental. The average duration of action and the blood concentration at the time of righting reflex were, for thiamylal, 94 min and 8.6 mg/L, respectively, and for thiopental, 54 min and 12 mg/L, respectively. Potency based on these concentrations indicated that thiamylal was 1.4 times more potent than thiopental.

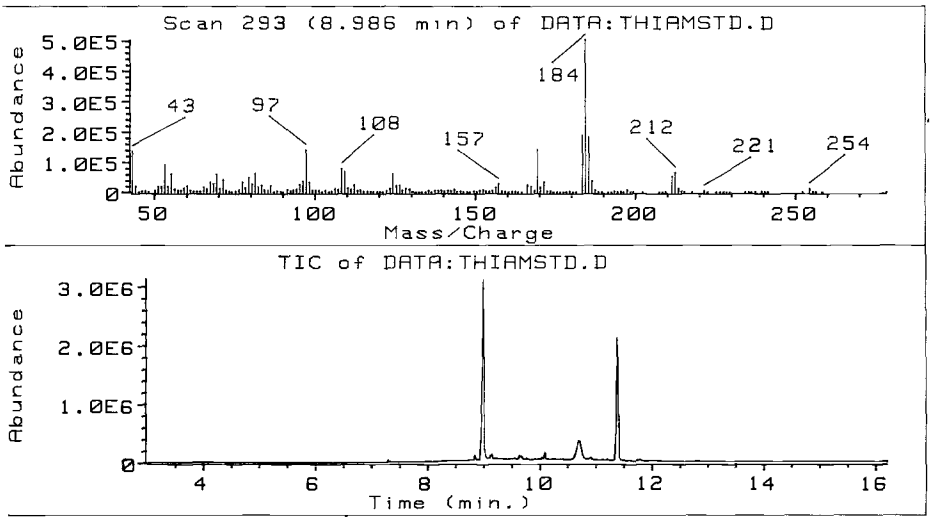

FIG. 2—*Total ion chromatogram and mass spectrum of a thiamylal standard.*

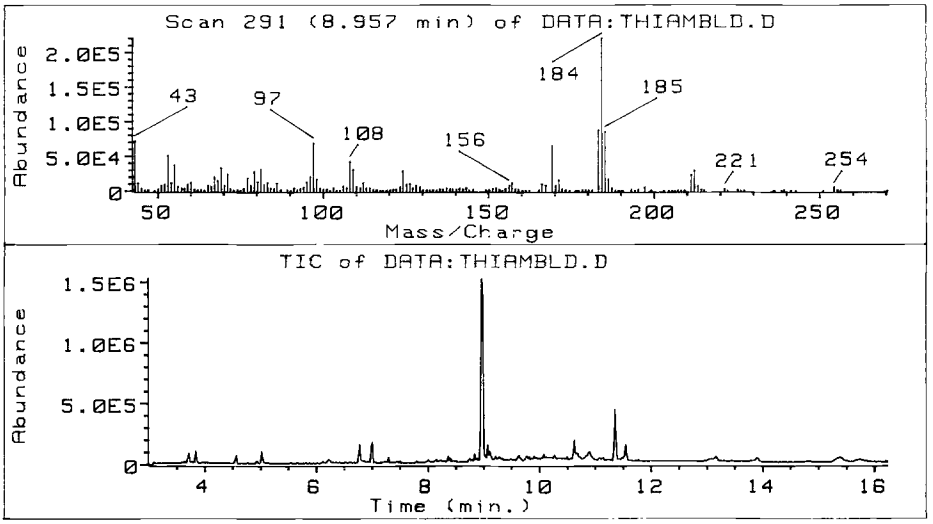

FIG. 3—*Total ion chromatogram and mass spectrum of thiamylal extracted from blood.*

Kelly et al. also noted that the shape of the blood concentration curves was similar, indicating nearly equal rates of elimination from the plasma. The peak blood concentration of 35 mg/L was reached at approximately 1 min after injection. The concentrations declined to 25 mg/L in 3 to 5 min and further to 15 mg/L at 20 min. These concentrations leveled off to 10 mg/L at 1 h and 5 mg/L at 4 h. Wyngaarden et al. [*8*] found thiamylal to be 1.5 times more potent than thiopental based on the duration of anesthesia from the onset of unconsciousness to the return of the righting reflex. Stephen and Martin [*9*] compared thiamylal and thiopental in clinical trials and found, based on the rate of induction, that a 2% solution of thiamylal was equal in potency to a 2.5% solution of thiopental; hence, thiamylal was 1.25 times more potent than thiopental. These relative potencies may be used to assist in the interpretation of thiamylal blood concentrations. The concentration of thiopental necessary to induce coma has been reported to be 8 mg/L [*10*], and peak blood concentrations reached during surgical anesthesia have been reported to be between 30 and 50 mg/L [*11*]. The minimum lethal dose of thiopental is 1 g.

A direct comparison of plasma concentrations of thiamylal and thiopental was made by Brodie, who injected the same man intravenously on alternate weeks with 3 g of thiamylal or thiopental [*3*]. The peak blood concentrations for each drug was approximately 50 mg/L, and the blood concentration/time curves were nearly superimposable. The concentration of thiamylal and thiopental at 4 h was approximately 15 and 10 mg/L, respectively. Brodie observed that the plasma concentration/time curve for both drugs showed two distinct phases—an early phase lasting 2 to 3 h which exhibited a steep slope and a later phase with a more gradual slope. The early drop in plasma concentrations indicates rapid tissue localization, and the more gradual slope is a reflection of the slow metabolic rate of the drug. The rate of metabolic transformation for both drugs in this study was reported to be about 10%/h. The site for metabolic formation is mainly the liver for each drug. The findings are similar to those of an earlier study involving only thiopental in man [*12*]. Brodie also investigated the physiological disposition of the ultrashort-acting barbiturates by intravenously injecting dogs with 40 mg/kg of thiamylal and thiopental and sacrificing the animals 3 h later. The tissue : blood ratios for thiamylal and thiopental, respectively, in these dogs are given in Table 1.

TABLE 1—*Studies of thiamylal and thiopental reported in the literature.*

Experiment	Thiamylal	Thiopental
Relative potencies of the drugs by three separate investigators [7–9]	1.4 1.5 1.25	1.0 1.0 1.0
Peak blood concentrations after identical doses in the same man (3 g) [3]	50 mg/L	50 mg/L
Blood concentrations at 4 h following a 3-g dose in the same man [3]	15 mg/L	10 mg/L
Rate of metabolism after identical doses in the same man [3]	10%/h	10%/h
Peak blood concentrations after identical doses in dogs (20 mg/kg) [3]	35 mg/L	35 mg/L
Blood concentrations at time of regaining righting reflex in dogs dosed with 20 mg/kg	8.6 mg/L	12 mg/L
Tissue/blood ratios in dogs 3 h after a 40-mg/kg IV dose [3]:		
fat/blood	8.0	6.0
liver/blood	1.6	1.6
kidney/blood	0.9	1.2
lung/blood	0.9	0.8
spleen/blood	0.7	0.7
brain/blood	0.7	1.2
muscle/blood	1.3	1.3

Woods et al. [*13*] have studied the cardiotoxic effects of thiamylal and thiopental in heart-lung preparations as well as intact animals. They reported that thiamylal may be less toxic but is definitely not more toxic than thiopental. The cause of death with anesthetic doses of either drug is respiratory depression, and therapeutic accidents are a result of wide interindividual variability in such toxic responses [*13*]. The comparison of the two drugs is summarized in Table 1.

Since the blood concentration versus time curves and the physiological disposition of the two drugs in animals were similar, the toxicological data already accumulated from clinical and postmortem thiopental cases may be applied for the purpose of evaluating thiamylal blood and tissue concentrations.

Table 2 gives the thiamylal concentrations obtained in this case and compares them to a similar case (Case 1) of thiopental intoxication [*14*]. In both cases an infusion of drug was started and, as anesthesia was induced, another factor was added, contributing

TABLE 2—*Thiobarbiturate tissue concentrations and ratios in suicides which involved a second cause of death.*

Tissue	This Case	Case 1 [*14*][a]
Blood	29 mg/L	14 mg/L
Liver	135 mg/kg	114 mg/kg
Kidney	25 mg/kg	16.7 mg/kg
Stomach content	0.4 mg/20 mL	NA[b]
Bile	16 mg/L	NA
Urine	20 mg/L	NA
Liver/blood	4.7	8.1
Kidney/blood	0.9	1.2
Liver/kidney	5.4	6.8

[a]Thiopental was administered rectally, and drowning was a contributing cause of death.
[b]NA = not available.

to the cause of death. In the thiamylal case, a ligature that was placed around the neck tightened as the body slumped from unconsciousness. In Case 1, a rectal infusion was started as the subject lay in a bathtub full of water. The subject was found with her knees in the air and her head under water. Drowning may have been a contributing factor. The liver:blood, kidney:blood, and liver:kidney ratios are similar in each case, as are the tissue concentrations. An empty vial of thiopental sodium for injection labeled to indicate that the vial had contained 6.5 g was found near the body. In the thiamylal case, a 500-mL IV bottle of Surital 10 g still containing 200 mL of fluid was brought in with the body. The solution was to be analyzed several weeks later, but had developed yellow flocculations and a precipitate in the meantime. No attempts were made to resolubilize the drug, and the contents of the bottle were not analyzed. These two cases are unique in that not only was there a secondary cause of death, but the infusion continued for several minutes before death and was infusing at the time of death.

Tables 3 and 4 represent deaths involving thiopental in the clinical setting [*6*]. Table 3 gives blood and tissue concentrations and tissue:blood ratios for deaths which occurred either during the infusion of thiopental or a few minutes thereafter in preparation for surgery. The blood concentrations in Cases 3, 4, and 6 approach those in Table 2, but the liver concentrations are much lower. The kidney:blood ratios may be considered similar, whereas the liver:blood and liver:kidney ratios are much lower.

Table 4 gives three cases in which death occurred between 2.75 and 4.5 h after thiopental administration. The average blood, liver, and kidney concentrations are lower than those in either Tables 2 or 3. Price et al. theorize and support the fact that the liver:blood and kidney:blood equilibrium ratios after a single dose of thiopental are approximately 1:9 and 2:0, respectively [*15*]. These ratios are approached at approximately 30 min after

TABLE 3—*Anesthetic deaths shortly after the infusion of thiopental reported in the literature* [6].

Case	Time to Death After Anesthesia, h	Tissue Concentrations,[a] mg/L or mg/kg			Tissue Ratios[a]		
		B	L	K	L:B	K:B	L:K
2	0.0	1.8	5.1	2.1	2.8	1.2	2.4
3	0.0	17.9	33.8	. . .	1.9	. . .	. . .
4	0.0	7.5	11.1	6.3	1.5	0.8	1.8
5	0.25	20	32	17	1.6	0.8	1.9
6	0.3	26	66	16	2.5	0.6	4.1
AVERAGE		14.6	29.6	10.4	2.0	0.85	2.6

[a]B = blood, L = liver, K = kidney.

TABLE 4—*Distribution of thiopental in anesthetic deaths reported in the literature* [6].

Case	Time to Death After Anesthesia, h	Tissue Concentrations,[a] mg/L or mg/kg			Tissue Ratios[a]		
		B	L	K	L:B	K:B	L:K
7	3.0	3.7	5.1	4.1	1.4	1.1	1.2
8	4.5	1.2	1.8	3.2	1.5	2.7	0.6
9	2.75	2.7	11.2	5.4	4.1	2.2	2.1
AVERAGE		2.5	6.0	4.2	2.3	2.0	1.3

[a]B = blood, L = liver, K = kidney.

TABLE 5—*Distribution of thiopental in cases of intentional overdose.*

Case	Reference	Tissue Concentrations,[a] mg/L or mg/kg			Tissue Ratios[a]		
		B	L	K	L:B	K:B	L:K
10	[16]	141	84	61	0.6	0.4	1.4
11	[17]	285	440	195	1.5	0.7	2.2
12	[18]	392	430	. . .	1.1	. . .	. . .
AVERAGE		273	318	128	1.1	0.55	1.8

[a]B = blood, L = liver, K = kidney.

TABLE 6—*Comparison of average blood (mg/L) and tissue (mg/kg) concentrations and tissue:blood and liver:kidney ratios in deaths involving thiamylal and thiopental.*[a]

	N	B (mg/L or mg/kg)	L (mg/L or mg/kg)	K (mg/L or mg/kg)	L:B	K:B	L:K
Suicides involving a second cause of death [14]	2	22	124	21	6.4	1.0	6.1
Anesthetic deaths shortly after the infusion of thiopental [6]	5	14.6	29.6	10.4	2.0	0.85	2.6
Anesthetic death several hours after the infusion of thiopental [6]	3	2.5	6.0	4.2	2.3	2.0	1.3
Suicides involving thiopental only [16–18]	3	273	318	128	1.1	0.55	1.8

[a]N = number of cases represented, B = blood, L = liver, K = kidney.

the end of injection and may persist for more than 8 h. It may be deduced that the liver:kidney ratios should approach one at equilibrium. This is supported by the average tissue:blood and liver:kidney ratios.

Table 5 represents blood and tissue concentrations in suicides in which the only cause of death was thiopental administration [16–18]. All of these subjects were found with an infusion line in place and nearly empty infusion bottles. Although the tissue:blood and liver:kidney ratios were low when compared to the other cases, the blood concentrations alone are sufficient to implicate the role of the drug as the cause of death. Note also that the high tissue concentrations in these cases are evidence that death by thiobarbiturates alone allows for greater accumulation of the drug in the body tissues. Table 6 summarizes the average tissue and blood concentrations and tissue:blood and liver:kidney ratios in these cases. We may conclude that the physiological disposition of thiamylal and thiopental is similar and that liver:blood and liver:kidney ratios may be greatest in suicides in which there was a secondary cause of death.

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