CASE REPORT

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A Fatality Involving Phentermine

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ABSTRACT: A case is presented where phentermine, a sympathomimetic amine used as an anorectic drug, is believed to have significantly contributed to the death of an individual in whom other drugs were also found. Blood, urine, and tissue concentrations of phentermine are reported and compared to other cases in the literature.

KEYWORDS: toxicology, phentermine, death

Phentermine (Fastin®) is a phenylethylamine with pharmacologic effects similar to amphetamine. It is available in 8-, 15-, and 30-mg slow release capsules and the recommended dose for the treatment of obesity is one capsule one to three times per day [*1*]. Most of the absorbed phentermine is excreted unchanged in the urine, with a small amount identified as the hydroxylated or conjugated metabolites [*2-3*]. The toxic effects of phentermine are extensions of its therapeutic effects and include restlessness, hyperactivity, tachycardia, hypertension, anorexia, nausea, vomiting, and diarrhea. There are few reports in the literature of fatalities caused by phentermine overdosage [*4,5*]. Because of the increased use of both nonprescription and prescription anorectic drugs, it is likely that these drugs will appear more frequently as causes of accidental and intentional overdoses. A case report is presented where phentermine is believed to have significantly contributed to the death of an individual even though other drugs were also present.

Case Report

A 32-year-old white male was allegedly given 2 chlorpromazine tablets by his father before going to bed. He was found dead the next morning. The decedent had been under psychiatric treatment for approximately five years. Although no specific diagnosis had been made, depression was considered and he was not viewed as suicidal. He had abused drugs in the past and was trying to lose weight with phentermine.

External examination of the body revealed a 1.6-m, 111-kg, normally developed male with no evidence of recent medical intervention or injury. Internally, little was observed that was

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outside of normal limits. The parenchyma of the lungs was markedly edematous and congested but without focal lesions or pulmonary emboli. The liver showed early active cirrhosis with diffuse macro-and micro-globular fatty metamorphosis, triaditis, and portal fibrosis. The kidneys and pancreas showed autolytic changes. The brain was mildly swollen. All other tissues and organs were unremarkable.

Experimental Procedure

Materials

Phentermine hydrochloride was obtained from Beecham, Inc., and a 200-mg/L solution in methanol as the free base was prepared.

Methyprylon was obtained from Roche Laboratories and a 10-mg/L solution in isopropanol served as the internal standard.

Sodium bicarbonate (Baker) solution was prepared by dissolving 8.4 g into a total of 100 mL of distilled water.

Dichloromethane and *n*-butyl chloride were Fisher pesticide grade. Anhydrous ether was Baker reagent grade.

Sulfuric acid and ammonium hydroxide were both ACS reagent grade and obtained from Matheson Scientific and Fisher Scientific, respectively.

Instrumentation

A Hewlett-Packard 5880 gas chromatograph equipped with a nitrogen phosphorus detector was used. Helium was the carrier gas at a flow rate of 30 mL/min. The column (2-m by 2-mm internal diameter) was packed with 3% OV-17 on 100–120 mesh Supelcoport. The oven temperature was programmed beginning at 140°C, increased by 25°C/min to 250°C, holding for 2 min at 250°C, and then increasing by 30°C/min to 325°C. The injection port temperature was 275°C and the detector temperature was 330°C.

Phentermine Analysis

Five millilitres of blood, urine, or tissue homogenate (1 g of tissue to 4 mL of bicarbonate solution) were adjusted to pH 9 with 2 mL of bicarbonate solution and extracted with 21 mL of *n*-butyl chloride : ethyl ether (3 : 1). After shaking for 10 min and centrifuging, the organic layer was removed and extracted with 3 mL of 1*N* sulfuric acid. Two millilitres of the acid layer were alkalinized with 0.5 mL of concentrated ammonium hydroxide and extracted with 5 mL of 1,2-dichloromethane. Four millilitres of the organic layer were removed and evaporated to dryness. The residue was reconstituted with 0.2 mL of internal standard solution and 4 μL were injected into the gas chromatograph. The retention time for phentermine was 1.5 min; the retention time of the internal standard was 3.7 min. Quantitation was based on the area ratio of phentermine to internal standard in comparison to fortified blood, urine, or tissue standards.

Results and Discussion

The blood submitted in this case was screened for: (1) ethanol, methanol, isopropanol, and other volatiles by gas chromatography; (2) ethchlorvynol, chloral hydrate, salicylates, and acetaminophen by color tests; (3) barbiturates, glutethimide, and carbamates by thin-layer chromatography, and; (4) basic drugs by gas chromatography. No alcohols or other volatiles were detected. The color tests revealed the presence of ethchlorvynol which was confirmed and quantitated by gas chromatography. The thin-layer chromatograms suggested amobarbital which was confirmed and quantitated by gas chromatography. The basic drug screen yielded a

TABLE 1—*Phentermine concentrations reported in the literature.*[a]

Specimen	Case Number						
	1	2	3	4	5	6	7
Blood, mg/L	7.6	1.5	0.9	3.0	1.6	0.8	0.5
Bile, mg/L	positive[a]	7	6.5	N.R.	N.R.	N.R.	N.R.
Liver, mg/kg	14	15	4.0	1.8	1.2	1.1	0.6
Kidney, mg/kg	16	12	N.R.	N.R.	N.R.	N.R.	N.R.
Stomach contents, mg	16	22	3	1.9	N.R.	N.R.	N.R.
Urine, mg/L	88	150	5.0	13.0	N.R.	N.R.	N.R.
Other drugs in blood (mg/L if reported)	amobarbital, 10 ethchlorvynol, 12	none	none	none	ethanol, 1300	amitriptylene nortriptyline diphenhydramine	propoxyphene ethanol, 1400
Cause of death	multiple drug intoxication	phentermine overdose	acute myocarditis	N.R.	N.R.	N.R.	N.R.
Reference	this study	[4]	[5]	[8]	[8]	[8]	[8]

[a]a = not quantitated and N.R. = not reported.

peak on the gas chromatogram which coeluted with phentermine and confirmation was achieved by performing a Toxilab® analysis on the remaining blood extract and comparing to a phentermine standard. Chlorpromazine was not detected in the blood. The concentrations of phentermine, amobarbital, and ethchlorvynol in the available specimens are listed in Table 1. Phentermine was detected in the bile but was not quantitated because no specimen remained after the initial screening. No other basic drugs were detected.

Hinsvark et al [6] reported peak blood phentermine concentrations of 0.09 mg/L after a single oral dose. Price [5] found a blood concentration of 0.9 mg/L during chronic phentermine therapy. Thus, the blood phentermine concentration of 7.6 mg/L in the present case is clearly in the toxic range. However, phentermine cannot be considered as the sole cause of death because of the presence of two other drugs, amobarbital and ethchlorvynol, especially since the amobarbital concentration in the blood was also in the toxic range [7]. Rather, it is most probable that the combined action of all the drugs caused the death. Because of the limited history surrounding the death, the manner of death was undetermined.

Drug concentrations in biofluids and tissues from the present case are shown in Table 1, Case 1, and suggest that the drug is well distributed throughout the central body compartments. As expected, the greatest amount of drug was found in the urine since much of the drug is excreted unchanged. These findings were in agreement with the previously reported distribution studies (Table 1, Cases 2-7) involving phentermine. In Case 2, death was attributed to an overdose of phentermine; in Case 3, the cause of death was acute myocarditis. No other drugs were detected in the blood in either Case 2 or 3, but salicylates and codeine were detected in the urine of Case 3. The data from the Registry of Human Toxicology [8] offered no history as to the cause of death; hence only blood and liver phentermine concentrations were provided when the drug was found. Blood to liver drug ratios vary greatly and are presumably related to the time between ingestion and death. In the present case, the relatively large amount of drug in liver compared to the blood and the relatively small amount of drug remaining in the stomach suggest that enough time passed between ingestion and death to permit absorption of most of the ingested drug.

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