

CASE REPORT

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Deaths As a Result of a Combination of Codeine and Glutethimide

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ABSTRACT: Toxicological findings are described in 16 medical examiner cases directly related to the combination of codeine and glutethimide. The cases described represent a six-month period, July through December 1982, showing the epidemic rate of abuse of this drug combination, most prominent in the Newark, NJ area since the late 1970s. Concentrations of codeine and glutethimide, measured by gas liquid chromatography (GLC), in the blood averaged 0.62 and 4.07 mg/L, respectively. Similarly determined urine concentrations averaged 38.06 and 12.68 mg/L, respectively. Specific concentrations of each drug in most cases were in the high therapeutic range, suggesting a possible toxic synergistic effect.

KEYWORDS: toxicology, codeine, glutethimide

Each year since the late 1970s there has been a high number of deaths in New Jersey caused by the oral ingestion of codeine and glutethimide. The highest incidence of such deaths has occurred and still occurs in the city of Newark. The drug combination is locally known as a "hit" and "consists of the oral combination of 60 mg of codeine, usually as aspirin, phenacetin, and caffeine with codeine, and 500 mg of glutethimide" [1]. Recently there have been reports of similar drug abuse in the cities of Los Angeles [2] and Chicago². The combination of codeine and glutethimide is used primarily in the 15- to 29-year age group and is believed to be an inexpensive, readily available, oral substitute for heroin [1].

Materials and Methods

Tissue samples were prepared by homogenizing 20 g of tissue with 60 mL of water.

Opiates were extracted by taking 1 mL of sample (2 mL for blood), spiked with 20 μ L of nalorphine (100 μ g/mL), plus 1 mL of 2N hydrochloric acid, and hydrolyzing for 30 min at 90°C. After cooling and centrifuging, the supernatant was transferred to a clean glass culture tube. The supernatant was then made basic with 1 mL of 0.1M carbonate/bicarbonate buffer

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pH 8.7 plus 20 μL of concentrated ammonium hydroxide and extracted with 10 mL of chloroform: isopropanol (4:1). After centrifuging, the aqueous layer was aspirated and the organic solvent pipeted into a clean glass culture tube. Two millilitres of 1N sulfuric acid were added and the mixture shaken for 5-min. After centrifuging, the aqueous layer was transferred to a clean glass culture tube. The aqueous solution was made basic with 1 mL of 0.1M carbonate/bicarbonate buffer pH 8.7 and 200 μL of concentrate ammonium hydroxide and extracted with 5 mL of chloroform: isopropanol (4:1). After centrifuging, the aqueous layer was aspirated and 4 mL of the solvent were pipeted into a clean culture tube and evaporated to dryness. Fifty microlitres of ethyl acetate and fifty microlitres of *N,O*-bis(trimethylsilyl)-trifluoroacetamide (BSTFA) reagent were added. The tube was covered and heated at 90°C for 20 min. The tube was then uncapped and dried on a concentrator. The final residue was dissolved in ethyl acetate and used for gas chromatography.

Glutethimide was extracted by adding to 1 mL of sample: 20 μL of aprobarbital (0.5 mg/mL), 1 mL of 0.1M phosphate buffer pH 7.0, and 5 mL of ethyl acetate. The mixture was shaken for 5 min and centrifuged. The ethyl acetate layer was transferred to a clean tube and evaporated to dryness. Three millilitres of 0.1N hydrochloric acid were added to the residue, the mixture vortexed, and then extracted two times using one-millilitre portions of hexane. After aspirating the hexane to waste, 5 mL of chloroform were added and the mixture shaken and centrifuged. The aqueous phase was aspirated to waste and the chloroform phase evaporated to dryness. The final residue was dissolved in ethyl acetate and used for gas chromatography.

Analysis

Opiate concentrations (Table 1) were determined with a Hewlett-Packard 5840A gas chromatograph, equipped with a 1.8-m (6-ft), 3% OV-101 on 80-100 Supelcoport column, operated isothermally at 240°C. A nitrogen phosphorus detector was used. The carrier gas was helium (30 mL/min) and the gases used for the detector were hydrogen (3.0 mL/min) and air (50 mL/min).

Glutethimide concentrations were determined with a Hewlett-Packard 5710A gas chromatograph, equipped with a 1.8-m (6-ft), 3% OV-101 on 80-100 Gas Chrom Q column, operated isothermally at 190°C. A flame ionization detector was used. The carrier gas was nitrogen (40 mL/min) and the gases used for the detector were hydrogen (30 mL/min) and air (30 mL/min).

Results and Discussion

Table 2 shows the range for the codeine concentration in blood to be 0.07 to 2.03 mg/L with an average value of 0.62 mg/L. The range for the codeine concentration in urine is 0.78 to 108.5 mg/L with an average value of 38.06 mg/L. Previously published reports have indicated a therapeutic concentration of codeine in blood to be 0.03 to 0.117 mg/L and toxic levels to be 1.0 to 8.8 mg/L [3,4]. The values obtained in most "hit" cases, therefore, fall in the high therapeutic range.

Similarly, the range for glutethimide concentration in blood is 0.4 to 15.1 mg/L with an aver-

TABLE 1—Distribution of morphine.

Case	Blood, mg/L	Urine, mg/L	Bile, mg/L	Liver, mg/kg	Kidney, mg/kg
A	0.04	43.21	24.39	0.34	...
B	0.09	9.25	23.50
C	0.14	35.57	39.56	...	0.35
D	0.37	3.04	50.54	...	0.49

TABLE 2—Medical examiner cases from June through December 1982.

Codeine, mg/L	Blood Morphine, mg/L	Glutethimide, mg/L	Codeine, mg/L	Urine Morphine, mg/L	Glutethimide, mg/L
0.07	0.09	1.00	0.78	0.14	2.60
0.13	...	3.00	61.00
1.06	...	15.10	22.10
0.44	0.29	3.10	5.93	2.02	...
0.47	0.07	4.90	4.60
2.03	...	1.50
0.38	...	0.50	108.50	9.20	6.10
0.07	...	1.30
1.22	0.04	6.40	8.75	0.43	3.20
0.64	...	2.10
0.42	...	0.40	4.04	1.24	0.70
0.30	...	3.20	9.20
0.97	0.07	6.80	58.40	2.80	...
0.77	0.21	5.00	71.00	34.00	5.40
0.46	...	6.80	47.10	10.60	11.90
Avg. = 0.62	Avg. = 0.13	Avg. = 4.07	Avg. = 38.06	Avg. = 7.55	Avg. = 12.68

TABLE 3—Distribution of codeine.

Case	Blood, mg/L	Urine, mg/L	Bile, mg/L	Vitreous, mg/L	Brain, mg/kg	Liver, mg/kg	Kidney, mg/kg	Spleen, mg/kg	Stomach Contents, mg
A	0.38	150.13	3.93	1.86	...	1.06	0.06
B	0.85	83.89	12.72	2.00	2.32
C	0.02	101.48	1.10	0.98	1.48	1.29	1.74	0.96	4.93
D	0.12	31.32	...	0.73	0.32	0.32	0.24

TABLE 4—Distribution of glutethimide.

Case	Blood, mg/L	Urine, mg/L	Bile, mg/L	Vitreous, mg/L	Brain, mg/kg	Liver, mg/kg	Kidney, mg/kg	Spleen, mg/kg	Stomach Contents, mg
A	5.05	23.82	6.66	0.25	...	13.44	0.04
B	9.70	9.11	32.25	3.40	19.52
C	3.04	5.60	8.42	1.95	7.48	11.40	6.00	4.36	8.96
D	1.90	4.07	8.81	1.90	2.03	6.97	3.54	21.6	...

age of 4.07 m/L. The range for glutethimide in urine is 0.70 to 61.0 mg/L with an average of 12.68 mg/L. Reported therapeutic concentrations for glutethimide in blood are 1.3 to 7.0 mg/L and toxic levels in the range 5 to 120 mg/L, with moderate intoxication occurring around 45 mg/L [3,4]. Again, the concentrations of glutethimide in most "hit" cases fall in the high therapeutic range.

It appears that the combination of codeine and glutethimide potentiate each other, producing a lethal comatose state at unpredictably low levels (Tables 3 and 4). To prevent the continued abuse of this drug combination, as well as the combination's lethal effect, it is hereby suggested that production of the drug glutethimide be discontinued. Where a sedative-hypnotic drug is therapeutically required, other preparations such as the benzodiazepines could be substituted.

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