CASE REPORT

Miftah Kemal,[1] *M.S.; Riazul Imami,*[2] *M.D., Ph.D.; and Alphonse Poklis,*[3] *Ph.D.*

A Fatal Methocarbamol Intoxication

REFERENCE: Kemal, M., Imami, R., and Poklis, A., **"A Fatal Methocarbamol Intoxication,"** *Journal of Forensic Sciences,* JFSCA, Vol. 27, No. 1, Jan. 1982, pp. 217-222.

ABSTRACT: A fatal methocarbamol intoxication is presented. Significant toxicologic findings were blood concentrations of 525 mg/L methocarbamol and 140 mg/dL ethanol. Analysis was by thin-layer, gas-liquid, and high pressure liquid chromatography. Toxicology data relevant to the interpretation of case findings are discussed.

KEYWORDS: toxicology, methocarbamol, chromatographic analysis, gas-liquid chromatography, high pressure liquid chromatography, ultraviolet spectrophotometry

Methocarbamol [2-hydroxy-3-(*o*-methoxyphenoxy)propyl 1-carbamate] is a carbamate derivative indicated for relief of discomfort associated with acute, painful, skeletomuscular conditions. The mechanism of action of methocarbamol has not been established in man, but may be due to central nervous system depression [*1*]. There is little in the literature concerning methocarbamol overdose in man [*2*]. This communication presents a case of fatal methocarbamol intoxication.

Case History

The decedent, a 37-year-old white female, had a history of marital problems. On the evening prior to her death, she had an argument with her current husband and her sons from a previous marriage who resided with their father. She then locked herself in a bedroom and started drinking alcohol. Early the following morning the husband knocked on the door and, receiving no answer, broke in and found her lying on the floor. He immediately called an ambulance, which took her to a local hospital where she was pronounced dead. The decedent had available the following medication: Synalgos-DC® (aspirin, phenacetin, caffeine, promethazine, and dihydrocodeine mixture) and Robaxin®-750 (methocarbamol).

Presented to the Toxicology Section at the 33rd Annual Meeting of the American Academy of Forensic Sciences, Los Angeles, CA, 18 Feb. 1981. Received for publication 9 March 1981; revised manuscript received 29 June 1981; accepted for publication 2 July 1981.

[1]Toxicologist, Office of the Medical Examiner, Charlotte County, Port Charlotte, FL.

[2]Director, Clinical Laboratories, Fawcett Memorial and St. Joseph Hospitals, and chief medical examiner, Charlotte County, FL.

[3]Assistant professor in forensic and environmental toxicology, Department of Pathology, St. Louis University School of Medicine, St. Louis, MO.

Autopsy Report

The decedent was a 37-year-old female 164 cm (5 ft 4½ in.) tall and weighing approximately 55 kg (185 lb). The autopsy failed to reveal any gross abnormalities other than bilateral edema and congestion of lungs, stomach mucosa, and spleen. The liver showed some fatty changes and the heart displayed slight evidence of arteriosclerotic disease. Blood, gastric contents, and urine were collected for toxicologic analysis.

Toxicology Findings

Comprehensive analysis of the gastric contents and urine disclosed methocarbamol and the ingredients of Synalgos-DC. However, only trace amounts of the Synalgos-DC mixture were present in blood and urine. Gas-liquid chromatographic (GLC) [*3*] and colorimetric [*4,5*] analyses of blood revealed only subtherapeutic concentrations of these compounds, indicating an overdose of Synalgos-DC had not been ingested (Table 1). The blood ethanol concentration, as determined by gas chromatography [*6*], was 140 mg/dL. Methocarbamol was determined by several analytical methods.

Thin-Layer Chromatography

Gastric contents and urine were made basic with ammonium hydroxide and extracted with diethyl ether. The ether was dried with anhydrous sodium sulfate and evaporated. The residue was dissolved in 1 mL of methanol from which aliquots were evaporated, redissolved in methanol, and applied to the thin-layer chromatography (TLC) plates (20- by 20- by 0.25-cm silica gel on glass, Analtech, Newark, DE). The residues and appropriate standards were developed in ethyl acetate, methanol, and ammonium hydroxide (85:10:5) [*7*]. Methocarbamol was visualized as a black spot by being sprayed with furfural and then concentrated hydrochloric acid followed by being heated at 110°C for 5 min [*8*]. The R_f of methocarbamol was 0.40, and the R_{fx} relative to codeine, 1.25.

Ultraviolet Spectrophotometry

Acidified gastric contents and blood were extracted with ether. The ether was washed with 5% bicarbonate and extracted with sodium hydroxide. Absorbance maxima at 221 ($E^{1\%}_{1cm}$, 370) and 272 ($E^{1\%}_{1cm}$, 100) with an inflection at 275 nm were noted in 0.5*N* sodium hydroxide extract. No shift in the absorbance maxima was noted at pH 2, pH 7, pH 9.5 or pH 11, indicating the presence of methocarbamol. The ultraviolet spectra of extracted methocarbamol are presented in Fig. 1.

TABLE 1—*Results of toxicologic analysis.*

Drug	Blood	Gastric Contents	Urine
Methocarbamol	525 mg/L	3.4 g	575 mg/L
Ethanol	140 mg/dl	...	...
Caffeine	ND[a]	positive	positive
Dihydrocodeine	ND	positive	positive
Phenacetin	ND	positive	positive[b]
Promethazine	ND	positive	ND
Salicylate	20 Mg/L[c]	positive	positive

[a]Not detected.
[b]Detected as acetaminophen.
[c]Analysis by UV spectrophotometry [*16*].

Gas-Liquid Chromatography

The quantitation of methocarbamol in blood and urine was by the GLC procedure for barbiturates as described by Kananen et al [*9*]. To a Teflon®-capped culture tube the following were added: 1.0 mL of blood or standards, 0.5 mL of 1*M* phosphoric acid, and 5.0 mL of 5 mg/L of aprobarbital (internal standard) in toluene. The mixture was shaken for 2 min and then centrifuged for 10 min. The toluene layer was then transferred to a Concentratube (Laboratory Research Co., Los Angeles, CA) into which 0.025 mL of methanolic trimethylanilinium hydroxide was slowly added by a syringe while being shaken in a vortex-mixer. The mixture was centrifuged for 10 min; then 1 μL of the methanol layer was injected into a Model 3920 Perkin-Elmer gas chromatograph equipped with a flame ionization detector and coupled to a PEP-2 data system. The sample was chromatographed in a 1.8-m (6-ft) by 6.25-mm outer diameter by 2-mm inner diameter glass column packed with 3% OV-1 stationary phase. The temperature conditions were as follows: column temperature, initially 140°C and then programmed at 16°C/min to 220°C; injector, 250°C; and detector, 300°C. The gas conditions were air, 50 mL/min; nitrogen, 30 mL/min; and hydrogen, 20 mL/min.

Methocarbamol was added to drug-free blood to prepare standards in a concentration range of 50 to 300 mg/L. The standards yielded a linear correlation with the aprobarbital internal standard. The retention time of methocarbamol was 6.0 min, and the retention time relative to aprobarbital was 1.35 min. As previously reported with other carbamate derivatives, methocarbamol apparently undergoes thermal decomposition in the injection port of gas chromatographs [*10,11*]. The retention time of the breakdown product was 6.5 min. Recovery of methocarbamol added to drug-free blood was approximately 70%. A typical chromatogram is presented in Fig. 2.

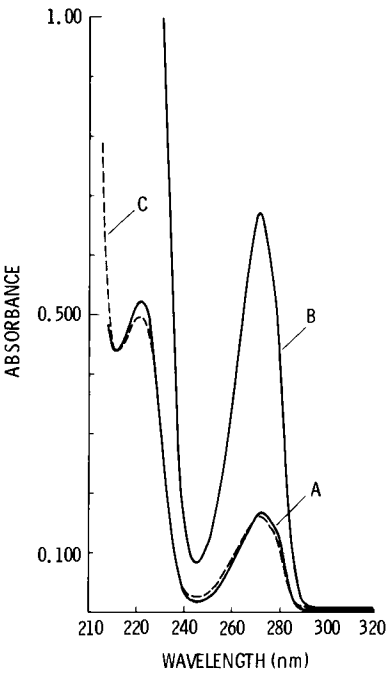

FIG. 1—*Methocarbamol UV spectra:* (A) *15 mg/L in 0.5*N *sodium hydroxide;* (B) *gastric contents extract in 0.5*N *sodium hydroxide; and* (C) *15 mg/L in 0.1*N *sulfuric acid.*

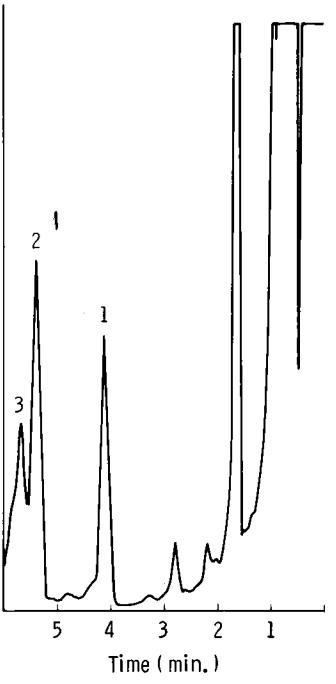

FIG. 2—*Gas-liquid chromatogram of urine extract, attenuation 4 × 100;* (1) *aprobarbital internal standard;* (2) *575 mg/L methocarbamol, one-third dilution; and* (3) *methocarbamol breakdown product.*

High Pressure Liquid Chromatography

Methocarbamol was also determined by a modification [*12*] of the reverse-phase high pressure liquid chromatographic (HPLC) blood drug-screening method of Kabra et al [*13*]. Two hundred microlitres of acetonitrile containing 15 μg of hexobarbital (internal standard) were added to 200 μL of blood in a 0.5-mL polypropylene centrifuge tube (Walter Sarstedt No. 72-699). The mixture was mixed in a vortex for 20 s and then centrifuged for 2 min at 15 000*g* (Eppendorf No. 5412). An aliquot of 12.5 μL of the clear supernatant was injected into a Model U6K valve attached to a Model 204 HPLC equipped with a variable wavelength detector (Waters Associates). The sample was chromatographed by reverse-phase HPLC; precolumn and analytical columns were octadecylsilane (ODS) as stationary phase (Waters, μ-Bondpack, C, 30 cm by 4 mm). The mobile phase was acetonitrile/phosphate buffer (14.5:85.5 by volume). The samples were eluted at a rate of 3.0 mL/min at 60°C and monitored at 210 nm with a sensitivity of 0.02 absorbance full scale.

Methocarbamol was added to drug-free blood to prepare standards at a concentration range of 10 to 75 mg/L. The standards yielded a linear correlation with the hexobarbital internal standard. Sample blood was diluted before the analysis to produce a response within the analytical range. The retention volumes V_r for methocarbamol and hexobarbital were 9.6 and 24.0 mL, respectively (Fig. 3). The V_r values, in millitres, of other drugs of toxicologic interest were these: salicylate, 3.6; acetaminophen, 6.0; caffeine, 7.2; methyprylon/phenobarbital, 8.4; ethchlorvynol, 18.0; amobarbital/pentobarbital, 27.6; secobarbital, 36.0; and methaqualone, 55.2.

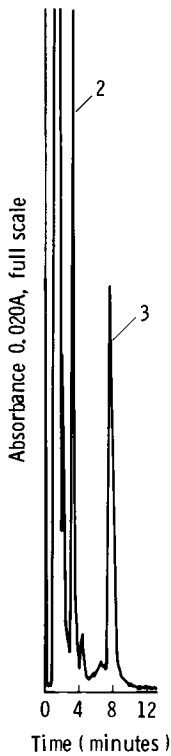

FIG. 3—*High pressure liquid chromatogram of blood extract:* (1) *aspirin, phenacetin, and caffeine mixture and blood peak;* (2) *500 mg/L methocarbamol, one-tenth dilution; and* (3) *15 mg/L hexobarbital internal standard.*

Summary

Fatalities associated with methocarbamol are rare. A review of the published literature and other toxicology reference sources yielded only two previous reports, both in the *Registry of Human Toxicology* [*2*]. One case was a "drug-induced" death with a blood concentration of 148 mg/L methocarbamol and 140 mg/dL ethanol. The other case was a "drug-related" death with the following blood concentrations: methocarbamol, 33 mg/L; morphine, 0.7 mg/L; and codeine, 0.13 mg/L. In controlled clinical studies peak plasma concentrations of methocarbamol following ingestion of 2 and 4 g were 25.8 and 41 mg/L, respectively [*14,15*]. In the case presented, blood values of methocarbamol were 13 times peak therapeutic concentrations and 3 times previously reported toxic concentrations. The ethanol present would be expected to contribute to the central nervous system depressant effects of methocarbamol. Given the case history, the lack of pathologic findings, and the results of toxicologic analyses, the cause of death was attributed to fatal intoxication from ethanol/methocarbamol ingestion.

The gas chromatographic procedure was developed for the determination of barbiturates. Methocarbamol and its breakdown product will interfere with the detection of amobarbital and pentobarbital. The authors recommend ultraviolet spectrophotometry or HPLC for confirmation of the presence of methocarbamol in blood. The observed results of GLC and HPLC agreed within 5%.

Acknowledgment

The authors thank A. H. Robins Co., Richmond, VA, for generously supplying the methocarbamol standards.

References

[*1*] Huff, B. B., Ed., *Physicians' Desk Reference*, 34th ed., Medical Economics Co., Orandell, NJ, 1980, p. 1436.

[*2*] *Registry of Human Toxicology*. American Academy of Forensic Sciences, Toxicology Section, Colorado Springs, CO, 1978.

[*3*] Garriott, J. C. and Latman, N., "Drug Detection in Cases of 'Driving Under the Influence,'" *Journal of Forensic Sciences*, Vol. 21, No. 2, April 1976, pp. 398-415.

[*4*] Frings, C. S., "Colorimetric Methods for the Quantitative Determination of Acetaminophen in Serum," *Clinical Toxicology*, Vol. 15, No. 1, Jan. 1979, pp. 67-73.

[*5*] Trinder, P., "Rapid Determination of Salicylate in Biological Fluids," *Biochemical Journal*, Vol. 57, 1954, pp. 301-303.

[*6*] Dubowski, K. M., "Ethanol, Type C Procedure," in *Methodology for Analytical Toxicology*, 2nd ed., I. Sunshine, Ed., CRC Press, Cleveland, OH, 1975, pp. 149-154.

[*7*] Davidow, B., Petri, N. L., and Quame, B., "A Thin Layer Chromatographic Procedure for Detecting Drug Abuse," *American Journal of Clinical Pathology*, Vol. 50, No. 6, Dec. 1968, pp. 714-719.

[*8*] Zingales, I., "Systemic Identification of Psychotropic Drugs by Thin Layer Chromatography. Part 1," *Journal of Chromatography*, Vol. 31, No. 2, Dec. 1967, pp. 405-419.

[*9*] Kananen, G., Osiewicz, R., and Sunshine, I., "Barbiturate Analysis—A Current Assessment," *Journal of Chromatographic Science*, Vol. 10, No. 5, May 1972, pp. 283-287.

[*10*] Martis, L. and Levy, R. H., "GLC Determination of Meprobamate in Water, Plasma and Urine," *Journal of Pharmaceutical Sciences*, Vol. 63, No. 6, June 1974, pp. 834-837.

[*11*] Finkle, B. S., "The Identification, Quantitative Determination, and Distribution of Meprobamate and Glutethimide in Biological Material," *Journal of Forensic Sciences*, Vol. 12, No. 4, Oct. 1967, pp. 509-528.

[*12*] Sprague, K. and Poklis, A., "Determination of Barbiturates in Postmortem Blood by High Pressure Liquid Chromatography: A Comparison with a Differential Ultraviolet Spectrophotometric Method," *Canadian Society of Forensic Science Journal*, Vol. 13, No. 1, March 1980, pp. 31-36.

[*13*] Kabra, P. M., Koo, H. Y., and Marton, L. J., "Simultaneous Liquid Chromatographic Determination of 12 Common Sedatives and Hypnotics in Serum," *Clinical Chemistry*, Vol. 24, No. 4, April 1978, pp. 657-662.

[14] Huf, E. G., Coles, F. K., and Eubank, L. L., "Comparative Plasma Levels of Mephenesin, Carbamate and Methocarbamol," *Proceedings of the Society of Experimental Biology and Medicine*, Vol. 102, 1959, pp. 276-277.

[15] Forist, A. A. and Judy, R. W., "Comparative Pharmacokinetics of Chlorphenesin, Carbamate and Methocarbamol in Man," *Journal of Pharmaceutical Science*, Vol. 60, No. 11, Nov. 1971, pp. 1686-1688.

[16] Williams, L. A., "Salicylate (Salicylic Acid), Type B Procedures," in *Methodology in Analytical Toxicology*, I. Sunshine, Ed., CRC Press, Cleveland, OH, 1971, pp. 307-308.

Address requests for reprints or additional information to
Miftah Kemal
Office of the Medical Examiner, Charlotte County
590 Olean Blvd. Suite #3
Port Charlotte, FL 33952