CASE REPORT

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A Fatal Interaction of Methocarbamol and Ethanol in an Accidental Poisoning

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ABSTRACT: A case is presented of a fatal drug interaction caused by ingestion of methocarbamol (Robaxin®) and ethanol. Methocarbamol is a carbamate derivative used as a muscle relaxant with sedative effects. Therapeutic concentrations of methocarbamol are reported to be 24 to 41 μg/mL. Biological fluids were screened for ethanol using the Abbott TDx system and quantitated by gas-liquid chromatography (GLC). Determination of methocarbamol concentrations in biological tissue homogenates and fluids were obtained by colorimetric analysis of diazotized methocarbamol. Blood ethanol concentration was 135 mg/dL (0.135% w/v) and urine ethanol was 249 mg/dL (0.249% w/v). Methocarbamol concentrations were: blood, 257 μg/mL; bile, 927 μg/mL; urine, 255 μg/mL; gastric, 3.7 g; liver, 459 μg/g; and kidney, 83 μg/g. The combination of ethanol and carbamates is contraindicated since acute alcohol intoxication combined with carbamate usage can lead to combined central nervous system depression as a result of the interactive sedative-hypnotic properties of the compounds.

KEYWORDS: toxicology, alcohol, methocarbamol, fatal drug interaction, ethanol

Methocarbamol (Delaxin®, Marbaxin®, Robaxin®), 1,2-propane-diol, 3-(2-methoxyphenoxy)-1-carbamate, is clinically used as a skeletal muscle relaxant with sedative properties. It has also been approved by the Food and Drug Administration (FDA) for control of the neuromuscular manifestations of tetanus (that is, intermittent tonic spasms of voluntary muscles and convulsions) [*1*]. The precise pharmacological mechanism of action of methocarbamol has not been determined, but the carbamates have been demonstrated to produce central nervous system (CNS) depression. The CNS depressant effects have

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been shown to occur preferentially with spinal and supraspinal polysynaptic reflexes. Methocarbamol has no direct action on the contractile mechanism of striated muscle, the skeletal-muscle endplate or the nerve fiber [*1,2*].

Methocarbamol can be administered intravenously or intramuscularly in single doses of 1 to 3 g. Total dose should not exceed 3 g/day for more than three consecutive days except in the treatment of tetanus. Methocarbamol is available for injection in 10-mL vials of 100 mg/mL. Initial oral dosage of methocarbamol for muscle spasm is 1500 mg q.i.d. followed by a maintenance dosage ranging from 750 mg q. 4 h to 1500 mg t.i.d. Total oral dosage can range from 4 to 8 g/day. Tablets are available in 500 and 750 mg. Robaxisal® tablets are marketed which contain 400 mg of methocarbamol and 325 mg of aspirin [*1,3*].

No toxic or lethal blood methocarbamol concentrations have been established [*4,5*]. A single dose of up to 12 g of methocarbamol has been given to adults without serious toxicity.[3] Toxicities resulting from overdosage of methocarbamol include nausea, drowsiness, blurred vision, fever, hypotension, convulsion, and coma [*4*]. The carbamates do produce CNS depression, which, if severe enough, can result in death. Additive or synergistic CNS depression can occur when carbamates are combined with ethanol [*6*]. Acute alcohol intoxication can increase the half-life of the carbamates [*7*], while it may inhibit oral absorption by up to 20% [*8*]. The CNS depression is insignificant or mild if alcohol intake does not exceed one or two drinks (90 to 120 mL of 100-proof whiskey) and if a single carbamate dosage is from 200 to 400 mg. Enhanced CNS depression will occur if the dosage of either drug is greater and may thus be sufficient to produce death [*6*].

Fatal methocarbamol overdose or methocarbamol interactions have been rarely reported [*9,10*]. This report describes a fatal interaction involving methocarbamol and ethanol.

Case History

A 31-year-old white male was found dead in a wooded area behind his home following a rain with a prescription bottle for Robaxin (methocarbamol, 750-mg tablets) which was partially filled with a milky white fluid and a Pepsi bottle approximately half full. The victim had on his person two containers of prednisolone optical solutions.

Materials and Methods

Specimen Collection

Blood (60 mL) was collected by cardiac puncture of the ventricles and stored in six (10-mL) Vacutainer® tubes: two sterile tubes, two tubes with potassium ethylenediaminetetraacetate (K_3EDTA), and two tubes with sodium fluoride and potassium oxalate. Bile and urine were collected by bladder punctures and stored in plastic specimen containers. Gastric contents (500 mL) were collected and stored in a plastic specimen container. Liver and kidney tissues (100 g each) were collected and stored in plastic, heat-sealed bags. The prescription bottles and Pepsi bottle with contents were submitted as found to the laboratory. Plasma or serum was separated by centrifugation at 2000 rpm for 10 min. Biological fluids were stored at 2° to 4°C, while tissues were stored at −70°C until analysis.

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Analytical Methods

Blood and urine specimens as well as the prescription and Pepsi fluids were screened for ethanol using the Abbott TDx®-Radiative Energy Attenuation (REA®) Ethanol assay. Ethanol quantitations were determined by gas-liquid chromatography [*11*]. The biological fluids, gastric contents, and prescription and Pepsi fluids were screened for the presence of numerous acidic, basic, and neutral drugs and metabolites including narcotics and other analgesics; barbiturates and other sedative hypnotics; benzodiazepines; cannabinoids; cocaine; phencyclidine; phenothiazines; sympathomimetic amines and tricyclic antidepressants by a combination of thin-layer chromatography (TLC), gas chromatography (GC), gas chromatography/mass spectrometry (GCMS), enzyme immunoassays (that is, enzyme multiplied immunoassay [EMIT] and fluorescence polarization immunoassay [FPIA]), and specific colorimetric procedures. Positive methocarbamol screens were confirmed using TLC with identification by chemical reaction and visualization with furfural and hydrochloric acid [*12*]. Determination of methocarbamol concentrations in the biological tissue homogenates (1:2 w/v), biological fluids, and prescription fluids were obtained by colorimetric analysis of diazotized methocarbamol by the method of Titus et al. [*13*].

Results

The biological fluid and tissue concentrations of ethanol and methocarbamol are given in Table 1. No other drugs were detected in any of the specimens. The optical prescriptions were found to be standard solutions of prednisolone. The milky white fluid in the prescription bottle labeled Robaxin was analyzed and found to contain methocarbamol. Analysis of the Pepsi specimen did not contain any measurable concentration of ethanol, and drug screening only detected the presence of caffeine.

Pathological Findings

Complete autopsy revealed acute obstructive emphysema and acute bronchitis with focal pneumonia. Aspiration of vomitus had occurred, and the bronchi contained some vomitus which contained a fine, particulate, milky white substance. The amount of vomitus in the airways was not occluding, and sufficient space was available for adequate air passage. A 9.5-cm old midline lumbar surgical scar was observed. No evidence of recent

TABLE 1—*Tissue and fluid concentrations.*

Body Fluid or Tissue	Concentration
	ETHANOL
Blood	135 mg/dL (0.135% w/v)
Urine	249 mg/dL (0.249% w/v)
	METHOCARBAMOL
Blood	257 μg/mL
Urine	255 μg/mL
Bile	927 μg/mL
Gastric	3700 mg
Liver	459 μg/g
Kidney	83 μg/g

trauma was found. Histological examination revealed acute passive congestion with acute bronchitus, focal acute bronchopneumonia with intraalveolar exudation of polymorphonuclear leukocytes, and edema fluid with minimal fibrin or mononuclear inflammatory response. Pneumonia was peribronchially located and associated with acute bronchial inflammation and hyperplasia of goblet cells. Cerebral sections revealed diffuse, mild to moderate congestion, and edema.

Discussion and Conclusions

The blood ethanol concentration of 135 mg/dL (0.135% w/v) is indicative of an ingestion of a significant quantity of ethanol (estimation of at least five 30-mL drinks of 100-proof whiskey in this 63-kg [140 lb] individual) which could produce CNS depressant effects. The greater concentration of ethanol in the urine than in the blood (249 versus 135 mg/dL, respectively) producing a ratio of 1.8 indicates that the victim was in a postethanol absorption phase at the time of his death.

Analysis of the Pepsi specimen revealed the presence of caffeine, a constituent of the cola beverage, but a lack of any measurable concentration of ethanol. The findings indicate that the victim most probably did not consume his ethanol from this specimen. The victim's presence in the rain may have also produced the milky white fluid from the Robaxin tablets in the prescription bottle, though preparation of the solution by the victim cannot be ruled out.

Maximum plasma methocarbamol concentration ranges from 16 to 41 μg/mL with single doses of 1 to 4 g [*1,14*]. Repeated administration of 1500 mg q. 6 h to steadystate has produced a maximum plasma concentration of 21 μg/mL (ranging from 10.8 to 30 μg/mL) and an average concentration of 8.4 μg/mL. Single oral doses of 3 g have produced an average maximum plasma concentrations of 46.3 μg/mL (ranging from 27.9 to 71.2 μg/mL) and caused only transient gastric upset, lightheadedness, and headache.[3] The concentration of methocarbamol in the blood (Table 1) exceeds the reported therapeutic range by approximately ten times. The reported methocarbamol concentration represents the ingestion of a significant quantity of methocarbamol regardless of the effects the victim's acute ethanol intoxication may have had on the methocarbamol pharmacokinetics. Ingestion of a large quantity of methocarbamol could produce toxicities, including nausea and vomiting, which resulted in the methocarbamol in the vomitus in the oral cavity and airways. Emesis of part of the ingested methocarbamol would indicate that an even larger amount than what remained in the gastric contents (3.7 g) had originally been ingested. The concentrations of methocarbamol in the tissues and other biological fluids further support this fact.

Only three other lethal overdoses have been reported (Table 2). Evaluation of the doses and biological distributions of methocarbamol in this case and the others previously reported reveals that all the doses exceeded the recommended daily dosages, but were

TABLE 2—*Methocarbamol concentrations in fatal cases.*

Blood, μg/mL	Brain, μg/g	Liver, μg/g	Urine, μg/mL	Gastric, g	Other Drugs[a]
320	133	296	. . .	3.4	secobarbital 55 μg/mL [*9*]
525	. . .	. . .	575	3.4	ethanol 0.14 g/dL [*10*]
109	. . .	. . .	. . .	6.0[b]	ethanol 0.29 g/dL[c]

[a]Blood concentrations.
[b]Estimated dose.
[c]Personal communication with Dr. Justine A. Jokl, M.D., A. H. Robins Company, Richmond, VA, 1989.

less than the maximum tolerated single dose (that is, 12 g), and that the plasma concentrations detected were in excess of the therapeutic concentration range. The methocarbamol in all cases has been acutely combined with a second drug, either alcohol or another sedative/hypnotic. The combination of methocarbamol and ethanol in this case proved sufficient to produce a lethal CNS depression. Based on the normal daily doses and the maximum tolerated dose, the dose of methocarbamol alone probably would not have been adequate to produce death.

The concentrations of methocarbamol and ethanol in this case, as well as the two previously reported, would exceed the concentration limits of Shinn and Shrewsbury [6] for production of insignificant or mild CNS depression by this drug interaction. Consumption of 90 to 120 mL of 100-proof whiskey, as proposed by Shinn and Shrewsbury, would produce a maximum blood ethanol concentration of 75 to 101 mg/dL in the average 70-kg man, while ingestion of 200 to 400 mg of methocarbamol would produce a peak blood concentration of less than 10 μg/mL. The concentration of both ethanol and methocarbamol in this case exceeded these estimated concentrations and produced an enhanced CNS depression which was sufficient to cause death. Combination of this type of CNS depressive agent with methocarbamol, either with accidental or intentional overdose, should be questioned as a potentially toxic or lethal drug interaction if either substance's concentration meets or exceeds therapeutic concentration. Even at therapeutic dosages, enhanced sedation may occur.

The death in this case was due to cerebral anoxia produced by CNS respiratory depression as a result of an acute ethanol and methocarbamol intoxication.

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