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Carisoprodol-Related Death in a Child

Carisoprodol (*N*-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate), a congener of meprobramate, is recommended by its manufacturers as a centrally acting musculoskeletal relaxant with mild anticholinergic, antipyretic, and analgesic properties. Many authorities maintain that the beneficial effects of carisoprodol noted in the treatment of patients with muscle spasm of local origin are related more to modification of central pain perception than they are to muscle relaxant properties [*1,2*]. Drowsiness, vertigo, weakness, and lassitude have accompanied carisoprodol therapy, but these adverse effects occur infrequently in adults who are taking recommended dosages of 250 or 350 mg four times daily [*3*].

Information in the medical literature is limited concerning acute or chronic carisoprodol toxicity. Stimulation and depression of the central nervous system were the chief manifestations of acute carisoprodol poisoning in two soldiers who ingested 8.40 and 9.45 g of the drug [*4*]. Initial levels of carisoprodol in the sera of these patients were 3.7 and 3.8 mg/100 ml. Treatment included gastric lavage and supportive measures, but symptoms persisted until serum levels of the drug were below 3.3 mg/100 ml. Mild toxicity manifested by slight stupor was reported in another patient who had a carisoprodol blood level of 3.1 mg/100 ml [*5*]. Carisoprodol-related toxicity has not been reported in children, and deaths in adults have not been attributed to the drug.

Case History

A 4 years, 10 months old boy was in good health until the day of admission to Scott and White Memorial Hospital. At about 4:00 p.m. he had ingested approximately 3500 mg of carisoprodol (10 tablets,[3] 350 mg each). He seemed "drunk" while eating an adequate evening meal, but became stuporous shortly afterwards.

Physical examination in the emergency room revealed a semicomatose boy with normal vital signs who reacted only to painful stimuli. A cuffed endotracheal tube was inserted at 8:30 p.m. and the stomach was lavaged with normal saline. Specimens of blood, gastric washings, and urine were collected for drug assay. Laboratory values for a complete blood count, urinalysis, serum glucose, serum calcium, electrolytes, and blood gases were in the normal range.

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[3] RELA®, Schering Corp., 60 Orange St., Bloomfield, N.J. 07003.

In the intensive care unit the boy remained comatose until 3:45 a.m. (11 h after ingesting the drug), when he sat up, appeared alert, and vomited. As he lapsed back into a semicomatose state, his respiratory movements became labored and mild cyanosis developed. Because a roentgenogram of the chest showed bilateral diffuse infiltrates, steroid and antibiotic therapy was begun. Respiratory distress increased during the next two hours, and spontaneous respiratory efforts ceased at 6:30 a.m. Ineffective ventilation led to cardiac arrest. Cardiorespiratory resuscitation was temporarily successful, but gradual deterioration ensued. The patient died 36 h after admission.

Toxicology

Method

Samples (1 ml) of serum, gastric lavage, and urine were placed in three separate 50-ml test tubes. After 100 μl of internal standard (pentobarbital, 20 mg/100 ml) and approximately 20 mg of monobasic potassium phosphate and 20 ml of dichloromethane were added, the tubes were sealed with teflon-lined screw-on caps. The contents were agitated for 3 min and centrifuged (1000*g*) for 5 min. The aqueous phase (upper layer) was discarded by aspiration, and approximately 2 g of anhydrous sodium sulfate were added to the dichloromethane. The contents were agitated and centrifuged for an additional 5 min. Then the dichloromethane was decanted into another tube and evaporated to dryness in a 50°C water bath under a stream of air. Fifty μl of chloroform/methanol (1/1, volume/volume) were added to dissolve the residue, and 2-μl fractions were analyzed by gas chromatography (GC). Reference standards of carisoprodol and meprobamate were assayed in the same manner as the human specimens. The drugs were quantitated by peak-height ratios.

A chromatograph[4] equipped with flame ionization detectors and glass columns (6 ft by ¼ in. outside diameter) packed with 3% OV-1 and 3% OV-17 was used for the analysis. The carrier gas, nitrogen, was passed over a vial containing formic acid just prior to entering the injection ports. The temperature of the oven was held at 140°C for 1 min, programmed (24°/min) to a final temperature of 275°C, and held for 12 min. The injection port was 315°C and manifold 320°C. The carrier gas was adjusted so that pentobarbital had a retention time of 5.2 min on OV-17 and 5 min on OV-1.

Results

Drugs other than carisoprodol and its metabolites were not detected in our patient's samples (Table 1). A small quantity of metabolite was found in the serum and a large

TABLE 1—*Distribution of carisoprodol and metabolites.*[a]

Specimen	Carisoprodol, mg/100 ml	Meprobamate, mg/100 ml
Serum	3.64	1.5
Urine	2.44	16.64
Stomach contents[b]	9.5	0.0

[a] All samples were collected 4.5 h after the drug was ingested.

[b] Total volume of gastric contents was 155 ml (14.7 mg drug).

[4] Perkin-Elmer Model 900 Gas Chromatograph, Perkin-Elmer Corp., Norwalk, Conn. 06852.

quantity was noted in the urine. This metabolite had retention times (OV-1 and OV-17 columns) identical to those of the only significant metabolite (excluding unmetabolized meprobamate) found in the urine of two patients who had drug assays in this laboratory after ingesting only meprobamate.

Discussion

Two patients with acute carisoprodol toxicity who recovered in several hours were reported to have serum levels of 3.7 and 3.8 mg/100 ml [*4*]. The colorimetric procedure used to measure the total carbamates in these patients would not distinguish carisoprodol from its metabolites. In our patient, the sum of the two active components, carisoprodol and meprobamate, would yield a serum carbamate level of more than 5.1 mg/100 ml.

In the dog, carisoprodol is metabolized primarily to a compound tentatively identified as hydroxycarisoprodol. Hydroxymeprobamate and small quantities of meprobamate appear in the urine with only traces of the unchanged drug [*6*]. In man, about 90% of meprobamate is excreted in the urine as hydroxymeprobamate and as a glucuronide [*1*].

The presence of meprobamate in the serum and the high ratio of meprobamate to carisoprodol in the urine (Table 1) suggest that meprobamate is the principal metabolite of carisoprodol in humans. The only significant compound other than carisoprodol and meprobamate that was detected in our patient's serum and urine had the same GC properties as the major substance in the urine of two patients who had ingested only meprobamate. The metabolite in this instance of carisoprodol toxicity was tentatively identified as hydroxymeprobamate.

Summary

A child who ingested approximately 3500 mg of carisoprodol gradually deteriorated and died within 36 h. GC analysis of serum, urine, and gastric samples indicated that meprobamate was the principal metabolite of carisoprodol.

References

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