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CASE REPORT

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Fatal Cyclobenzaprine Overdose with Postmortem Values*

ABSTRACT: There are only two published cases of overdose with postmortem blood cyclobenzaprine concentrations, both with confounding factors. We report two additional cases of fatal cyclobenzaprine overdose with postmortem values. Case 1: a 56-year-old female was found in full cardiopulmonary arrest after a verbal suicide threat to a friend. Postmortem blood concentrations were cyclobenzaprine 0.96 mg/L and diazepam 0.3 mg/L. Case 2: a 37-year-old male was found in full arrest by a family member after an intentional ingestion of cyclobenzaprine. Postmortem blood concentrations were cyclobenzaprine 0.8 mg/L and ethanol 0.174 gm/dL. The concentrations of diazepam and ethanol reported in these two patients were not found in quantities usually associated with a fatal outcome, suggesting that the cyclobenzaprine was the primary cause of the fatality. Additionally, the blood was drawn from a femoral site, so that postmortem redistribution is not a likely factor. Blood concentration of $\geq$ 0.8 mg/L cyclobenzaprine may be associated with a fatal outcome.

KEYWORDS: forensic science, postmortem concentration, cyclobenzaprine, death, overdose

Cyclobenzaprine is a skeletal muscle relaxant, structurally related to amitriptyline, differing only by the presence of a double bond on the central ring (Fig. 1). While reports of cyclobenzaprine overdose are not uncommon, fatal cyclobenzaprine overdose reports are rare. In the past five years Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers reported 22 090 cyclobenzaprine exposures, with 15 180 treated in a hospital (69%) and only 36 fatalities (0.16%) (1–5). Two retrospective case series of cyclobenzaprine overdose, involving 434 patients, reported no fatalities (6,7). There are only three published reports of overdose with postmortem blood cyclobenzaprine concentrations (8–10). We report two additional cases with postmortem cyclobenzaprine concentrations.

Case 1

A 56-year-old 144 lb (65.3 kg) female was found in full arrest of unknown duration on a couch in her home by a friend. She had made a verbal suicide threat to a friend after marital discord and a separation from her spouse. Empty bottles of pills and a bottle of whisky were found next to the patient along with a suicide note. Resuscitation attempts by emergency response personnel and emergency department staff were unsuccessful. Autopsy revealed diffuse visceral congestion, mild cardiomegaly, moderate coronary artery atherosclerosis, evidence of a previous hysterectomy and appendectomy but no anatomical cause for death. Three pills were found in the stomach, but not identified. Postmortem blood concentrations, drawn from a femoral site, were cyclobenzaprine 0.96 mg/L and diazepam 0.3 mg/L. No other drugs, ethanol or volatiles were found.

Case 2

A 37-year-old, 149 lb (67.6 kg) male was in a physical altercation at a bar the night before death. He returned home and went to bed. At approximately 7 a.m. he woke up and took a "handful" of cyclobenzaprine and went back to bed. Five hours later he was found in full arrest by a family member. Resuscitation attempts by emergency response personnel and emergency department staff were unsuccessful. Autopsy revealed no significant trauma and no anatomical cause for death. Three small abrasions to the face and two abrasions to the right hand were noted consistent with the history of a recent altercation. Additionally, microscopic findings of the liver were consistent with chronic hepatitis C. Examination of the skull, neck, spine, shoulder girdle and pelvis failed to reveal fracture. There was no soft tissue hemorrhage within the scalp and no abnormalities in the brain after multiple horizontal sections. Postmortem blood concentrations, drawn from a femoral site, were cyclobenzaprine 0.8 mg/L and ethanol 0.174 gm/dL. No other drugs or volatiles were found.

Methods

Postmortem samples from both decedents were analyzed at the same state public health department laboratory. Results were confirmed by gas chromatography mass spectroscopy (GCMS). Blood is screened for four drugs/categories: acetaminophen, cyclic antidepressants, salicylates and barbiturates by florescence polarization immunoassay. Additionally it is screened for a larger group of compounds using GCMS. GCMS is used to confirm any findings and quantify the results.

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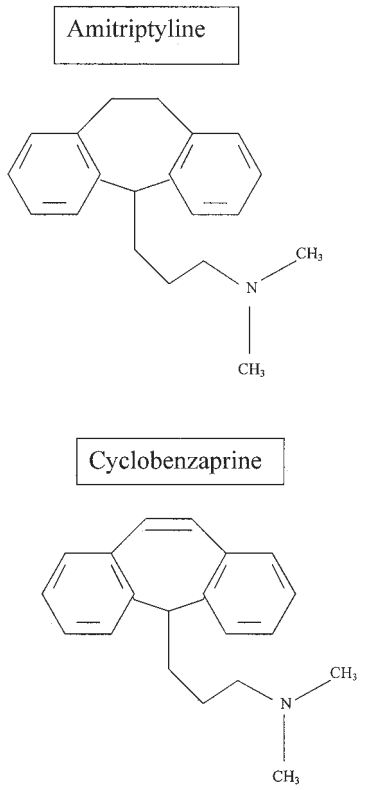

FIG. 1—*Structures of amitriptyline and cyclobenzaprine.*

Discussion

Blood concentrations of cyclobenzaprine from therapeutic dosing can vary from patient to patient. A regimen of 10 mg TID (30 mg/day) produced peak plasma concentrations of 18 to 49 ng/mL (0.018 to 0.049 mg/L) in 17 volunteers (11). A single 40 mg oral dose of cyclobenzaprine produced a mean peak plasma concentration of 26.7 ng/mL (SD +24.2) (0.0267 mg/L). The serum concentrations recorded in our two patients were 20 to 40 times greater than these therapeutic concentrations. One brief report of blood concentrations of cyclobenzaprine in overdose from emergency room patients recorded levels from 0.03 to 0.35 mg/L (12).

It is not known what dose our patients ingested to achieve such elevated serum concentrations, but our estimate is greater than 800 mg. Cyclobenzaprine is available in 10 mg size tablets only. Therefore our patients may have ingested 80 or more tablets each. This massive amount is in contrast with earlier reports. In previous retrospective studies, no deaths were reported (6,7). It was speculated that because of the small dose size of the 10 mg tablet, many patients did not ingest sufficient quantity to produce the life threatening effects commonly seen with the cyclic antidepressants (6,7).

Previous cases with postmortem cyclobenzaprine concentration have reported values of 0.3 mg/L to 1.786 mg/L (8–10). All cases have reported significant co-ingestants or circumstances that contributed to the fatal outcome. The concentrations of diazepam and ethanol reported in our two patients were not found in quantities usually associated with a fatal outcome, suggesting that the cyclobenzaprine was the primary cause of the fatality. Ethanol has been reported to potentiate the CNS depressant effects of cyclobenzaprine (13). However, even with a mild potentiation, a blood ethanol concentration of 0.174 g/dL is not expected to be in the fatal range. Our patient with a diazepam concentration of 0.3 mg/L is well within the expected concentration for a single ingestion of one 10 mg tablet (14). Patients overdosing on diazepam alone have recorded plasma concentrations as high as 4.79 mg/L with only sedation. Divoll et al. suggested that severity of poisoning following a benzodiazepine overdose is determined largely by the co-ingestant and not by the amount of benzodiazepine ingested or its concentration in plasma (15). It is unlikely that diazepam played a significant role in the fatality of Case 1.

Finally, the blood was drawn from a femoral site, so that postmortem redistribution is not a likely factor. Cyclobenzaprine does undergo some postmortem redistribution, but it is felt that the femoral site appears to remain the most reliable (10).

Conclusion

Blood concentration of $\geq$ 0.8 mg/L cyclobenzaprine may be associated with a fatal outcome. This report increases the number of postmortem values available for evaluation of cyclobenzaprine overdose cases.

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