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CASE REPORT

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Polydrug Fatality Involving Metaxalone

ABSTRACT: A 29-year old female with a history of depression was found dead in a hotel room. The death scene investigation found empty pill bottles and an empty liter bottle of wine. Metaxalone, a centrally acting muscle relaxant, along with citalopram, ethanol, and chlorpheniramine were identified in the postmortem samples and quantitated by gas chromatography-mass spectrometry. The concentration of metaxalone in femoral vein blood was 39 mg/L. The heart blood concentration was 54 mg/L. Femoral vein blood concentrations of citalopram and chlorpheniramine were 0.77 mg/L and 0.04 mg/L, respectively. Ethanol levels were 0.13 g/dL in vitreous and 0.08 g/dL in heart blood. Other tissue samples were also analyzed. The authors consider the metaxalone concentrations toxic and potentially fatal. The citalopram concentrations were lower than those reported in fatal cases for this drug alone. Death was ascribed to polydrug abuse/overdose with metaxalone a major contributor. This represents the first reported case to our knowledge in which a metaxalone overdose significantly contributed to death.

KEYWORDS: forensic science, forensic toxicology, metaxalone, citalopram, overdose

Metaxalone (Skelaxin®)[5-(3,5-dimethylphenoxymethyl)-2-oxazolidinone] is a widely used, orally administered, centrally acting skeletal muscle relaxant. It is prescribed widely for acute, chronic, traumatic, and inflammatory musculoskeletal disorders since its introduction in 1962 (1–3). Metaxalone is available as 400 mg tablets with the recommended dose being two tablets three to four times a day.

Since its introduction, little has been reported concerning the toxicity of metaxalone in humans. A review of the literature revealed no reported cases of fatal overdose with metaxalone as a sole agent or in combination with other drugs. Kious et al. (4) report a case of suicide involving multiple drugs causing serotonin syndrome. Metaxalone was detected in their case, but was not considered a contributory agent. The dose of metaxalone taken was 2400 mg, but no postmortem levels were specified.

Citalopram (Celexa®) is a selective serotonin reuptake inhibitor used to treat depression. It is administered at an initial dose of 20 mg daily, taken orally, and may be increased to 40 mg/day. Citalopram has been studied previously in fatalities (5,6) and has been reported previously in a multiple drug intoxication overdose case (7).

In this report, we discuss the first reported case of a fatality in which metaxalone played a major role.

Case History

A 29-year-old female with cartilage-hair hypoplasia (a syndrome of short-limbed dwarfism) was found dead in a hotel room that she had rented the prior day. She had a history of depression for about a year attributed to a recent break up of a personal relationship and employment difficulties. She had been abusing alcohol recently. She was found after she did not leave by check out time. The police were called and had to cut the security chain on the door to gain entry to the secured room. The decedent was lying on the bed. Two prescription bottles for forty 400 mg tablets of metaxalone were found with directions to take one tablet four times a day. One bottle was prescribed approximately seven months prior to death and was empty. The other was prescribed approximately six weeks prior and contained 21 tablets. Also, an empty liter wine bottle was on the nightstand. Otherwise, the scene was unremarkable. No suicide note was found.

The adult decedent weighed 71 lb. and was 41 in. in length, consistent with her history of dwarfism. She had a mild to moderate scoliosis of the thoracic vertebral column. Postmortem examination revealed the presence of multiple subacute superficial incised wounds involving the left anterior wrist. The larynx and trachea had small amounts of edematous fluid. Particulate white granular debris was present within the duodenum and proximal half of the small bowel. The remainder of the gross and microscopic examination was unremarkable.

Materials and Methods

Urine was screened for the presence of drugs of abuse on the Syva EMIT plus analyzer using EMIT reagents and calibrators according to the manufacturer, Syva, Palo Alto, CA. EMIT assays screened for benzoylecgonine, amphetamines, barbiturates, opiates, propoxyphene, tricyclic antidepressants, methadone.

Volatile analysis was performed on blood with a headspace procedure (8) using *n*-propanol as the internal standard. The column was a 6-ft Porapak S at a temperature of 180°C. Instrumentation was Shimadzu GC I4A, Kyoto, Japan.

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TABLE 1—*Postmortem drug concentrations.*

			Blood (mg/L)		Tissue (mg/kg)		Postmortem Contents (mg/TV)*	
	Vitreous (g/dL)	Urine (g/dL)	Femoral	Heart	Brain	Liver	Gastric	Duodenum
Metaxalone	na	na	39	54	163	195	75	164
Citalopram	na	na	0.77	1.17	1.6	7.5	0.2	0.02
Ethanol	0.13	0.13	na	0.08†	na	na	na	na
Chlorpheniramine	na	na	0.04	0.04	0.10	0.25	nd	nd
Caffeine	na	na	10.3	11.7	8.3	7.0	<0.5	<0.5

* TV = total volume.
na = not analyzed.
nd = not detected.
† = units are g/dL for ethanol in blood.

Alkaline drug screens by gas chromatography/mass spectrometry (GC/MS) were performed on blood, liver, and gastric contents. Five mL of blood, 0.1mL gastric contents and 1 g brain and liver was extracted with 10 mL of n-butyl chloride after adjusting the pH to 10 with NH_4OH. The organic layer was acidified by the addition of 5 mL of 1N HCl. The aqueous layer was made basic by the addition of 2 mL of concentrated NH_4OH and extracted with 0.2 mL CH_3Cl (9). Two μL of the CH_3Cl was injected into the Hewlett Packard 5971 GC/MS System (Palo Alto, CA) equipped with a 12.5 m by 0.2 mm HP-1 methyl silicone column. The column temperature was programmed from 70 to 280°C at 20°C/min. Helium carrier gas flow was 1 mL/min. A total ion scan was performed, in the scan mode from 40 to 400 mev. Specific ions used by MS for identification were 122 and 221 for metaxalone; 58, 238, and 324 for citalopram; 58, 203, and 167 for chlorpheniramine; and 109 and 194 for caffeine.

Metaxalone was quantitated using a multi-point standard curve from 5 to 20 mg/L with appropriate dilutions. Assays were performed in duplicate. Other drugs were quantitated by comparison to known drug standards. Analytical standards included metaxalone (Elan Pharmaceuticals) and citalopram Hbr (Forest Lab, Inc.). Other standards were obtained from Alltech (State College, PA) or Radian (Austin, TX).

Results and Discussion

Emit screening of urine was positive for benzodiazepines. GC analysis was positive for ethanol, and GC/MS analysis was positive for high doses of metaxalone and citalopram and lesser doses of chlorpheniramine and caffeine (Table 1).

Metaxalone is metabolized and excreted mainly in the urine (10). The half-life is 2–3 h and duration of action is 4–6 h (3). Metaxalone is considered a muscle relaxant with low toxicity. The exact mechanism of action in humans has not been established; however, it is hypothesized to act through central nervous system depression (3). Adverse reactions to prescribed doses include nausea, vomiting, drowsiness, dizziness, and irritability. An LD_{50} for rats has been determined at 1200 ± 173 mg/kg with symptoms of sedation, hypnosis and respiratory failure. An LD_{50} could not be established in dogs as high doses elicited emesis (11).

Under fasting conditions, the peak plasma concentration, $C_{max,}$ for an 800 mg oral dose of metaxalone has been found to be 4.0 mg/L in plasma (Personal Communication, PRACS Institute, Fargo ND). The level of metaxalone found in this case was well above this therapeutic level. Thus, we consider the dose of metaxalone found in this case to be toxic and potentially fatal.

The C_{max} of metaxalone 2 h after a usual dose of 800 mg has been reported in the literature to be 296 μg/mL (296 mg/L) (3). We question the accuracy of that concentration. Plasma levels do not reach 296 mg/L with an 800 mg dose according to the above information. Intuitively this also seems correct. If plasma volume were assumed to be 5L, an 800 mg dose would distribute to only 160 mg/L if there were neither redistribution nor effects of drug metabolism. Additionally, other drugs in class with metaxalone have peak plasma concentrations ranging from 1.65 to 30 μg/mL (mg/L) (3). We suggest that this therapeutic level of metaxalone reported in the literature is off by a factor of 100.

Citalopram was also found in this case. Daily oral doses of citalopram generally range between 20–40 mg. It has been reported that in adult patients receiving chronic daily doses of 40 mg, steady state plasma levels of citalopram averaged 0.079 mg/L (12). Multiple cases reported in the literature state that as a single agent citalopram overdose concentrations in whole blood range from 2.0–11 mg/L (6,13). Fu et al. reported a multiple drug overdose case where the femoral and heart blood levels were 0.88 mg/L and 1.16 mg/L, respectively (7). In this case, citalopram was above the therapeutic level but below the level consistent with fatal citalopram overdose as a single drug.

As noted, the decedent also had a blood ethanol level of 0.08 g/dL. While this level by itself would not be fatal, it would, nevertheless, contribute to the depressant effects of both the metaxalone and the citalopram. The level of chlorpheniramine, an antihistamine and central nervous system depressant, was minimally above the therapeutic range, 0.017 mg/L (14). However, it was well below the fatal level reported for this drug alone, 1.1 mg/L (15).

We report the case of a multiple drug overdose involving the centrally acting muscle relaxant metaxalone. Metaxalone was found in toxic/fatal levels in this case. We believe that the metaxalone significantly contributed to the decedent's death with additive depressant effects from citalopram, ethanol, and chlorpheniramine. This is the first such report that we are aware of involving significant metaxalone toxicity. The cause of death was certified as polydrug overdose/abuse with the manner of death being suicide.

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