Metaxalone (Skelaxin®)-Related Death

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Abstract

The case history and toxicological findings of a fatal multi-drug overdose involving metaxalone (Skelaxin) are presented. Gas-liquid chromatography with flame-ionization detection and gas chromatography–mass spectrometry were used to determine the following drug concentrations (mg/L) in aortic blood: 19 mg/L metaxalone; 190 mg/L acetaminophen; 0.28 mg/L hydrocodone; and < 0.1 mg/L diazepam, nordiazepam, amitriptyline, and nortriptyline. The following concentrations of metaxalone were reported in alternate specimens: 17 mg/L in femoral blood; 44 mg/L in bile; 70 mg/kg in liver; 7 mg/L in urine; 202 mg/kg in gastric contents; and 14 mg/L in vitreous humor. These concentrations were determined using both direct extraction and the method of standard addition. The quantitative results obtained by both procedures were in good agreement. Because of the limited information published on metaxalone toxicity, the pathologist assigned the manner and cause of death as accidental acute hydrocodone intoxication. Four additional cases in which metaxalone was present were analyzed for comparison. Two cases were probable drug-related deaths and had metaxalone aorta blood concentrations of 18 and 11 mg/L. The other two cases had therapeutic metaxalone concentrations in the aortic blood of < 0.75 and 2.1 mg/L.

Introduction

Metaxalone (Skelaxin) is a central nervous system (CNS) depressant utilized in the treatment of acute skeletal muscle pain. The mechanism of action has not been established; however, the mode of action is thought to be related to metaxalone’s sedative properties. Approved by the Food and Drug Administration in 1962, metaxalone taken orally at a therapeutic dose of 800 mg produces a peak plasma concentration of approximately 1.6–3.0 mg/L (1–3). Treatment usually involves therapeutic dosing ranging from 800 to 3200 mg daily. Approximately 27% of the dose is excreted unchanged in urine (4). Adverse reactions associated with metaxalone include drowsiness, dizziness, headaches, and GI distress (5,6).

Limited information has been published on metaxalone toxicity. A review of the literature indicates that there is presently one reported death in which the causative agent(s) included metaxalone with a reported concentration and one mention of metaxalone detected in a fatality, but concentrations were not given (7). To our knowledge, no therapeutic postmortem fluid and tissue values have been published.

We report a case of fatal overdose involving metaxalone. Concentrations of metaxalone were determined in body tissues and fluids by quantitative gas–liquid chromatography (GLC) with a flame-ionization detector (FID) following both direct extraction and the method of standard addition. Qualitative identification of metaxalone was performed by electron impact chromatography–mass spectrometry (GC–MS). Metaxalone concentrations were compared with four other cases where metaxalone was also present. Two of these cases were expected drug-related deaths in which metaxalone was detected and two had therapeutic metaxalone concentrations.

Case History

The deceased was a 21-year-old white female found dead in her bedroom. She was prescribed multiple medications including a prescription for Lorcet® (hydrocodone/acetaminophen), filled 3 days prior to her death, which had 42 pills missing. With the exception of minor findings at autopsy including a small pulmonary arterial thrombus in the left lung lobe, vertebral scoliosis, rib fractures (resuscitative), chronic gastritis, and pyelonephritis in both kidneys, gross pathological and histopathological findings were unremarkable. Postmortem fluids and tissues were collected and sent for toxicological analyses.

Toxicological Analyses

Sample preparation

No sample preparation was required for the blood, urine, and vitreous humor specimens. Bile and gastric content were diluted 1:10 with distilled water. Five grams of liver was diluted with 15 g of distilled water and homogenized with a Brinkman Polytron® Pt 3000 homogenizer (Westbury, NY). Aliquots of prepared specimens were then analyzed by the methods de-
scribed herein. When appropriate, aliquots were further diluted to assure linearity of results.

**GLC reagents**

Potassium acid phthalate/sodium hydroxide buffer (pH 5.0) was obtained from Fisher Scientific. Methylene chloride, acetonitrile, methanol, and hexane were all ACS grade or better.

**GLC standards**

A stock metaxalone standard (1000 mg/L) was prepared by dissolving 10.0 mg of metaxalone (Mallinckrodt, Hobart, NY) into a sufficient quantity of methanol to equal a 10-mL volume. A six-point calibration curve was prepared using 0 to 30 mg/L concentration in drug-free blood. Stock internal standard (1000 mg/L) was prepared by dissolving 10.0 mg of p-methylphenobarbital (Aldrich, Milwaukee, WI) into a sufficient quantity of methanol to equal a 10-mL volume. The working internal standard was prepared by diluting the stock standard 1:10 with methanol. Control metaxalone stock standard (1000 mg/L) was prepared similarly by a second analyst. Control blood specimens with target values of 2.5 mg/L and 7.5 mg/L were prepared from the control stock standard. Calibrators and controls were analyzed with each batch of samples.

**Direct extraction procedure**

Quantitative GLC analysis of metaxalone was based upon the work of Anderson and Fuller (8). Aliquots of 100 μL of working internal standard and 1 mL of calibrator, control, or sample were pipetted into separate 15-mL test tubes to which 1.0 mL of pH 5.0 potassium acid phthalate/sodium hydroxide buffer was added. The specimens were vortex mixed for 15 s, centrifuged at 3000 rpm for 5 min, and poured into a ChemElut™ 1003 Extraction Column-Tox Elut (Varian, Walnut Creek, CA). The drug was eluted from the column with two consecutive washes of 3.5 mL of methylene chloride. The methylene chloride was evaporated under nitrogen at 40°C and reconstituted with 100 μL of acetonitrile. The acetonitrile was washed 3 times with 500 μL of hexane. The acetonitrile was then placed in an autosampler vial, and 1 μL was injected into the GC.

Metaxalone blood concentrations were calculated from a linear regression of the calibrator responses based on the peak-area ratio (peak area of the metaxalone to that of the internal standard) with an average $r^2$ value of 0.998 ($n = 5$). Extraction recovery of metaxalone and p-methylphenobarbital (ISTD) were 71% and 77%, respectively ($n = 3$). All calibrator were with in 20% of their expected concentrations. The intrarun precision was less then 7.2% for all calibrators. The between-run precision was 11% for the 2.5 mg/L control and 5.5% for the 7.5 mg/L control ($n = 5$). None of the following compounds were found to interfere with metaxalone at 10 mg/L: butalbital, meprobamate, carisoprodol, theophylline, carbamazepine, topiramate, acetaminophen, phenobarbital, phenoobarbital, primidone, phenytoin, lamotrigine, oxcarbazepine, 10-hydroxycarbazepine, diazepam, and nordiazepam. The presented method for metaxalone had a lower limit of quantitation (LOQ) of 0.75 mg/L, and the limit of detection (LOD) was 0.25 mg/L and linear up to 30 mg/L.

**Standard addition procedure**

Three additional 1-mL aliquots of sample or sample homogenate were spiked with metaxalone at concentrations of 1.5, 5.0, and 10 mg/L (9). All specimens remained at room temperature for 4 h prior to extraction as described. Regression equations for each specimen yielded $r^2$ values of 0.990 or better.

**GLC instrumentation**

Analyses were performed on a Perkin Elmer AutoSystem GC (Boston, MA) equipped with a flame ionization detector. The detector response was recorded and integrated using TurboChrom Version 4.1. Chromatography was performed with a temperature ramp of 20°C/min starting at 120°C and climbing to 300°C on a 15-m × 0.53-mm × 1.5-μm DB-5, bonded-phase capillary column (Agilent, Wilmington, DE). Injection port and detector temperatures were 300°C. Gas flow rates were as follows: 18 mL/min for helium carrier gas; 45 mL/min for hydrogen; and 450 mL/min for air. Under these conditions, the metaxalone and internal standard retention times were 6.4 and 6.0 min, respectively. As depicted in Figure 1, the relative retention time (RRT) of metaxalone to the ISTD was 1.07.

**GC–MS**

Following direct extraction, a 1-mL aliquot was injected into the GC–MS. The GC was a Hewlett-Packard model 6890 with a split/splitless injection port connected to a Hewlett Packard 5973 mass selective detector with an electron ionization source. Agilent ChemStation version B.01.00 was used to control the operation of the GC–MS. The GC oven was programmed to an initial temperature of 120°C and a hold time of 2 min, followed by a 20°C/min ramp to a final temperature of 300°C to be held for 5.0 min. The total run time was 16.0 min. The injection
port and transfer line temperatures were 250°C and 280°C, respectively. The column was an Agilent DB-5MS capillary column (15 m x 0.25 mm, 0.25-μm film thickness). The MS was operated in the full scan mode. Tissue and blood extract spectra were compared with that of unextracted metaxalone. The metaxalone yielded the major fragments and relative abundance 122 (100%), 105 (29%), 91 (19%) and molecular ion 221 (62%) (Figure 2).

Results and Discussion

The results of the toxicological analyses by two different procedures (direct extraction and method of standard addition) are presented in Table I. The results between the two procedures are in good agreement and demonstrate the lack of matrix effects and ease of direct extraction of metaxalone from tissue matrices. Hence, metaxalone can be reliably extracted by the solid support extraction described. Although both GLC and GC–MS techniques readily detected metaxalone, the relatively high concentration of metaxalone even at therapeutic doses makes GC–FID sufficient for detection.

No therapeutic postmortem concentrations have been reported in the literature and only one case of a fatal/toxic metaxalone overdose was found (1). This paper reports postmortem metaxalone concentrations in five deaths.

In the presented case (case 1), aortic blood concentrations were as follows: 19 mg/L metaxalone; 190 mg/L acetaminophen; 0.28 mg/L hydrocodone; and < 0.1 mg/L diazepam, nordiazepam, amitriptyline, and nortriptyline. The hydrocodone liver concentration was 0.74 mg/kg. Diazepam, nordiazepam, amitriptyline, and nortriptyline were either therapeutic or subtherapeutic. Volatiles were analyzed for on a Perkin Elmer (Boston, MA) headspace. No volatile compounds were detected. Two additional cases yielded metaxalone concentrations in aortic blood of < 0.75 (case 2) and 2.1 mg/L (case 3), which are consistent with therapeutic concentrations in living individuals (Table II). Furthermore, two cases that were suspected drug-related deaths had elevated metaxalone concentrations of 11 (case 4) and 18 mg/L (case 5). Results of blood and tissue concentrations of the presented case (case 1), the expected drug-related cases (case 4 and 5) and the case from the literature (case 6) are compared in Table III. From the comparison, little to no significant postmortem redistribution occurred. In addition, these data support that metaxalone has a low apparent volume of distribution and that both blood and liver concentrations can assist in differentiating between an overdose and a therapeutic ingestion.

There was significant hydrocodone concentration in the blood and liver for the pathologist to rule the presented case (case 1) an acute hydrocodone death; postmortem blood concentrations of 0.13–7.0 mg/L have been reported in accidental or intentional overdose of hydrocodone (10). The pathologist did not report metaxalone as an agent contributing to this death largely because of the lack of reported toxic concentrations in the literature. Even though the metaxalone concentration by itself may not be fatal in the presented case, we believe that the supratherapeutic concentration of metaxalone, which has sedative and CNS depressant properties, contributed to the fatal intoxication in the presented case.

### Table I. Comparison of Direct Extraction Procedure to Method of Standard Addition

<table>
<thead>
<tr>
<th>Sample (mg/L or mg/kg)</th>
<th>Direct Extraction</th>
<th>Standard Addition</th>
<th>% Difference</th>
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<tbody>
<tr>
<td>Liver (presented case 1)</td>
<td>69.7</td>
<td>74.4</td>
<td>6.74</td>
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<tr>
<td>Liver (therapeutic case 2)</td>
<td>13.8</td>
<td>14.2</td>
<td>2.90</td>
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<tr>
<td>Liver (therapeutic case 3)</td>
<td>8.8</td>
<td>8.9</td>
<td>0.45</td>
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<tr>
<td>Bile (presented case 1)</td>
<td>43.9</td>
<td>40.9</td>
<td>-6.83</td>
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<tr>
<td>Gastric content (presented case 1)</td>
<td>202.6</td>
<td>232.9</td>
<td>14.96</td>
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</table>

### Table II. Postmortem Blood and Tissue Concentrations for Therapeutic Metaxalone Cases

<table>
<thead>
<tr>
<th>Sample (mg/L or mg/kg)</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood, femoral</td>
<td>2.8</td>
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<tr>
<td>Blood, aorta</td>
<td>&lt; 0.7</td>
</tr>
<tr>
<td>Liver</td>
<td>14</td>
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<tr>
<td>Urine</td>
<td>1.9</td>
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* na, not available.

### Table III. Postmortem Blood and Tissue Concentrations for Drug-Related Deaths Involving Metaxalone

<table>
<thead>
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<th>Samples (mg/L or mg/kg)</th>
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<tr>
<td>Blood, femoral</td>
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<tr>
<td>Blood, aorta</td>
<td>19</td>
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<tr>
<td>Bile</td>
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<tr>
<td>Liver</td>
<td>70</td>
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<td>Vitreous</td>
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<td>Urine</td>
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</table>

* na, not available.

References