Oxcarbazepine Overdose in a Polysubstance Related Suicide

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Oxcarbazepine Overdose in a Polysubstance Related Suicide

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Introduction

Oxcarbazepine is a derivative of carbamazepine that is used primarily in the treatment of epilepsy, and experimentally as a mood-stabilizer in adjunctive therapy for the treatment of bipolar disorder. Oxcarbazepine is converted through oxidation to its pharmacologically active metabolite 10-OH-Carbazepine, which is thought to be responsible for most of the anticonvulsant action of the drug. Adverse effects of oxcarbazepine are generally dose-dependent and may include fatigue, somnolence, dizziness, diplopia, nystagmus, and ataxia. Additive sedative effects have been noted when oxcarbazepine is used in combination with other CNS depression-producing medications. Furthermore, oxcarbazepine and 10-OH-Carbazepine are powerful CYP2C19 inhibitors, potentially increasing the plasma concentration and pharmacological response of CYP2C19 substrates such as diazepam. The therapeutic range for oxcarbazepine is based on the metabolite and extends from 6-35 μg/mL. Toxicity has been reported with 10-OH-Carbazepine levels as low as 65 μg/mL, and one fatality has been documented with a 10-OH-Carbazepine concentration of 92 μg/mL.

Hydrocodone is a narcotic analgesic that undergoes demethylation and reduction to produce several pharmacologically active metabolites, including hydromorphone, norhydrocodone, and dihydrocodeine (6-α-hydrocodol), which contribute to its efficacy. Hydrocodeone toxicity may be characterized by respiratory depression, drowsiness, and coma. Therapeutic blood and plasma concentrations of hydrocodeone typically range from 10-50 ng/mL, while levels greater than 100 ng/mL are considered toxic, and concentrations exceeding 200 ng/mL can be potentially fatal.

Diazepam is a benzodiazepine known for its efficacy and rapid onset. Therapeutic ranges of diazepam and its metabolite nordiazepam in blood and plasma measure between 200-2500 ng/mL. Diazepam toxicity may result in drowsiness, weakness, ataxia, and coma; however, serious and fatal effects are uncommon with diazepam if used singularly. Most terminal adverse events associated with diazepam are the result of interaction or combination with other drugs, especially CNS depressants.

Methods

Postmortem heart blood, femoral blood, urine, vitreous fluid, gastric contents, and liver and brain tissue were submitted for toxicological analysis. Routine screening of heart blood was performed using Enzyme Multiplied Immunoassay Technique (EMIT) and liquid-liquid alkaline extraction followed by gas chromatography/mass spectrometry (GC/MS) analysis. 10-OH-Carbazepine as well as hydrocodeone and its metabolites were quantified in femoral blood by an external laboratory using liquid chromatography/tandem mass spectrometry (LC-MS/MS). Diazepam and nordiazepam quantitation was performed on heart blood using high performance liquid chromatography (HPLC).

Results

<table>
<thead>
<tr>
<th>EIA (Heart Blood)</th>
<th>LC-MS/MS (Femoral Blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodeone (free)</td>
<td>180 μg/mL</td>
</tr>
<tr>
<td>Norhydrocodeone</td>
<td>6.1 ng/mL</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>47 ng/mL</td>
</tr>
<tr>
<td>Hydrocodeone</td>
<td>47 ng/mL</td>
</tr>
<tr>
<td>Dihydrocodeine (free)</td>
<td>490 ng/mL</td>
</tr>
<tr>
<td>Hydromorphone (free)</td>
<td>6.1 ng/mL</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>6.1 ng/mL</td>
</tr>
<tr>
<td>Norhydrocodeone</td>
<td>47 ng/mL</td>
</tr>
</tbody>
</table>

Conclusion

The most significant finding in this case is the 10-OH-Carbazepine concentration of 180 μg/mL, which is greater than the highest known fatal level of 92 μg/mL.

The cause of death in this case was ruled oxcarbazepine and hydrocodeone intoxication with diazepam use, and the manner of death was suicide.