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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.

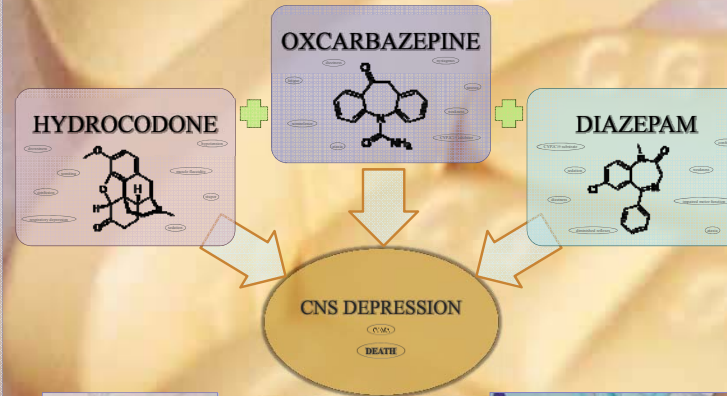
Hydrocodone is a narcotic analgesic that undergoes demethylation and reduction to produce several pharmacologically active metabolites, including hydromorphone, norhydrocodone, and dihydrocodeine (6- α -hydrocodol), which contribute to its efficacy. Hydrocodone toxicity may be characterized by respiratory depression, drowsiness, and coma. Therapeutic blood and plasma concentrations of hydrocodone 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.

Objective

To present a case of a polysubstance related suicide involving the synergistic effect of toxic concentrations of oxcarbazepine and hydrocodone in combination with the presence of diazepam.

To report the highest blood concentration of 10-OH-Carbazepine found in literature for a drug-related death investigation.



Case History

Presented in this case is a 67-year-old female with a history of depression, psychiatric hospitalization, and previous suicide attempts. The decedent was found lying supine in bed with a bottle of hydrocodone in one hand and a can of soda in the other, next to a suicide note. Several other prescription medications, including oxcarbazepine, gabapentin, diazepam, quetiapine, tizanidine, and lorazepam were found at the scene.

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 hydrocodone 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

EIA (Heart Blood)	LC-MS/MS (Femoral Blood)
Opiates	10-Hydroxycarbazepine: 180 µg/ml.
Benzodiazepines	11hydrocodone (free): 490 ng/ml.
GC/MS Screen (Heart Blood)	11hydromorphone (free): 6.1 ng/ml.
Oxcarbazepine	Dihydrocodeine/Hydrocodol (free): 47 ng/ml.
11hydrocodone	
Dihydrocodeine	HPLC (Heart Blood)
Diazepam	Diazepam: 465 ng/mL
Nordiazepam	Nordiazepam: 435 ng/mL
Acetaminophen	Diaz + Nordiaz Total: 900 ng/ml.

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 hydrocodone intoxication with diazepam use, and the manner of death was suicide.