CASE REPORT

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Olanzapine-Related Fatality

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ABSTRACT: A 43-year-old male psychiatric outpatient died within hours of ingesting as much as 600 mg of olanzapine, a newer antipsychotic agent related to clozapine. Analysis of postmortem blood and urine by gas chromatography with nitrogen-selective detection yielded olanzapine concentrations of 1238 and 6987 μg/L, respectively, greatly in excess of levels expected following therapeutic administration of the drug. Based on the toxicology findings, the decedent's known history of suicide attempts, and the circumstances surrounding the death, this case was ruled a suicide by olanzapine overdosage.

KEYWORDS: forensic science, forensic toxicology, forensic pathology, death, olanzapine, neuroleptic agent, antipsychotic agent, suicide, drug overdose

Olanzapine is a newer antipsychotic agent that resembles clozapine both chemically and pharmacologically. It is supplied as 2.5, 5, 7.5 or 10 mg tablets of the free base for oral administration; the usual adult dosage range is 5 to 20 mg daily (1). Trough plasma olanzapine concentrations in patients receiving 10, 15 or 20 mg of the drug daily on a chronic basis average 9.3, 19 and 26 μg/L, respectively (2). The time required to achieve peak plasma concentrations following an oral dose averages 5.1 h, and the elimination half-life averaged 30 h (3). Published procedures for determination of olanzapine in biological fluids have involved liquid chromatography with electrochemical detection (2,4,5). Acute overdosage with as much as 300 mg of the drug in an adult was reported to cause only drowsiness and slurred speech (1). To date, we are unaware of any reports of fatalities associated with acute overdosage of olanzapine.

Materials and Methods

Case History—A 43-year-old male psychiatric outpatient weighing 187 1b with a prior history of attempted suicide was in possession of a prescription vial issued to him five days earlier for 60, 10 mg olanzapine tablets, with instructions to take two tablets at bedtime. One evening at about 2200 to 2300 hours, he informed a friend he had ingested a quantity of these tablets. He was encouraged to vomit, which he did, and was then put to bed. At about 0130 to 0200 the next morning, he was believed to have ingested additional tablets. At 0500 he was heard snoring, but by 0800 he was unresponsive and paramedics were summoned. He was pronounced dead at the scene, and the medication vial was noted to be empty.

Postmortem Findings—An autopsy was conducted on the day after death. The principal findings were moderate pulmonary congestion and edema, as well as moderate macromodular cirrhosis of the liver.

Toxicological Analyses—A general screen for toxic drugs and chemicals was performed on blood and urine collected at autopsy using immunoassay, thin-layer chromatography and gas chromatography. Aside from olanzapine, the blood was found to contain 0.08 g/dL ethanol, 0.04 mg/L diphenhydramine and 0.57 mg/L trazodone.

Olanzapine Analysis—A pure reference standard of olanzapine was obtained through the courtesy of Eli Lilly and Company (Indianapolis, IN). A methanolic stock solution (1 mg/mL) of this drug was made and was used to prepare blood and urine spiked standards of 10, 50, 100 and 250 μg/L. The decedent's blood and urine were diluted tenfold and 100-fold, respectively, prior to analysis.

A 2 mL aliquot of blood or urine was combined with 100 μL of internal standard solution (1 mg/L flurazepam in water) and 2 mL of saturated sodium borate, and this mixture was extracted with 8 mL of n-butyl chloride. After centrifugation, the solvent extract was transferred to a clean tube and evaporated to dryness in a 60°C vortex evaporator. The residue was reconstituted in 50 μL of ethyl acetate and a 2 μL aliquot was injected into the gas chromatograph.

A Hewlett-Packard model 6890 gas chromatograph with nitrogen-selective detection was employed for quantitation. Using a 15 m HP-5 capillary column programmed from 150 to 300°C at 15°C/min increase, the retention times for olanzapine and flurazepam were 9.98 and 10.19 min, respectively. Calculation of olanzapine concentration was based on a response factor derived from a standard curve of peak height ratio of analyte/internal standard.

Quantitative confirmation was performed using a Hewlett-Packard model 6890/5973 gas chromatograph-mass spectrometer equipped with a 12 m HP-1 capillary column. The full-scan mass spectrum is shown in Fig. 1.

Results and Discussion

The concentrations of olanzapine found in the decedent's blood and urine, 1238 and 6897 μg/L, respectively, exceed by at least

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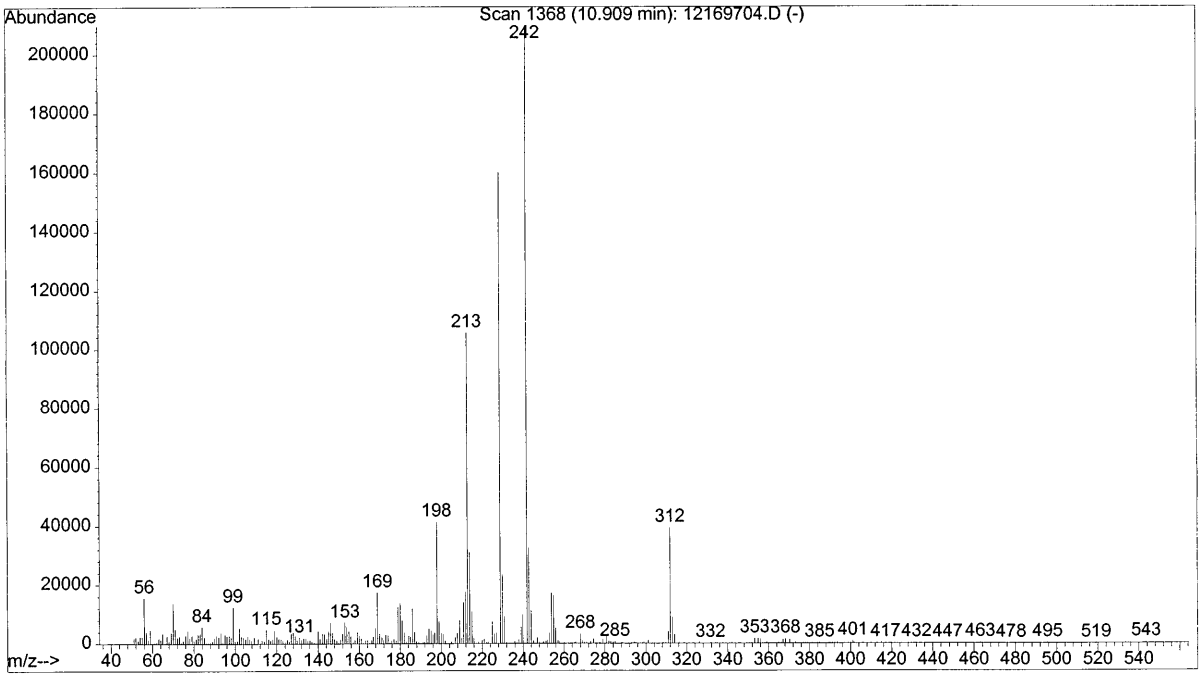

FIG. 1—*Olanzapine analysis: full-scan mass spectrum.*

100-fold the levels reportedly found at steady-state in patients receiving 10 mg daily of olanzapine on a long-term basis (2). We believe that these concentrations would have required the acute ingestion of nearly the entire contents of the olanzapine prescription vial, 600 mg, and based on this together with the decedent's known history of suicide attempts and his statements to witnesses, this case was ruled a suicide by acute olanzapine overdosage.

The product literature for olanzapine indicates that overdosage may result in obtundation, seizures, hypotension and circulatory collapse, although no documented instances of this have been reported (1). Olanzapine has been shown to behave as an antagonist of dopamine, serotonin, alpha-1-adrenergic, and muscarinic receptors (6). The recent report (7) of a 2.5-year-old child who ingested 10 mg of olanzapine accidentally and manifested constricted pupils, hypersalivation, drowsiness and agitation is most consistent with anticholinergic toxicity as the predominant clinical feature of overdosage with this drug. Severe intoxication may result in coma, respiratory depression, and loss of brain stem reflexes (8).

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