Case Report

An Overdose of Risperidone

Angela C. Springfield1 and Ed Bodiford2
1Chief Toxicologist, Tarrant County Medical Examiner’s District and Associate Professor of Pathology and Pharmacology, Institute of Forensic Medicine, University of North Texas Health Science Center, Fort Worth, Texas and 2Forensic Death Investigator, Tarrant County Medical Examiner’s Office, Fort Worth, Texas

Abstract

A fatality resulting from the suicidal ingestion of risperidone is described. The decedent had a lengthy history of mental illness but was otherwise healthy. Biological fluid samples obtained at autopsy were analyzed for risperidone by high-performance liquid chromatography. The blood concentration of risperidone was 1.8 mg/L, the urine concentration was 14.4 mg/L, and the concentration in the gastric contents was 34.6 mg/L (1.04 mg total). The 9-hydroxyrisperidone metabolite was not detected in the blood or gastric contents; however, the urine contained 17.8 mg/L of this metabolite.

Introduction

Risperidone is a novel antipsychotic agent belonging to a new chemical class, the benzoisoxazole derivatives. It is characterized by having a strong binding affinity for serotonin 5-HT2 receptors, a strong binding affinity for the catecholamine, dopamine (primarily dopamine-D2), and a high affinity for α1- and α2-adrenergic receptors and histamine H1 receptors (1). The drug is designed for the treatment of both positive (hallucinations, delusions, and thought disorders) and negative (emotional withdrawal, blunted effect, and loss of speech) symptoms of schizophrenia (2).

Risperidone undergoes extensive metabolism (hydroxylation and oxidative N-dealkylation), and its major metabolite, 9-hydroxy-risperidone, displays similar pharmacological activity to the parent compound. Oxidative metabolism of risperidone is subject to genetic polymorphism (3). The oral bioavailability varies from 66 to 82%. Peak plasma concentrations of risperidone, 3–8 µg/L, are achieved within 2 h of a single, 1-mg dose. The plasma concentrations of risperidone, 9-hydroxy-risperidone, and the active moiety (risperidone plus 9-hydroxy-risperidone) are linearly related to dosage (less than 25 mg per day) in schizophrenic patients (4).

Risperidone and its metabolites are extensively distributed throughout the body. Plasma protein binding of risperidone is approximately 90%, and the volume of distribution is 1.2 L/kg. The drug is primarily eliminated through the urinary route. Approximately 70% of the administered dose is recovered in the urine, and 15% is recovered in the feces over a 1-week period postdose. Plasma elimination half-lives (t1/2) of risperidone and 9-hydroxy-risperidone in extensive metabolizers are 2.8 and 20.5 h, respectively. The t1/2 for the active moiety is approximately 24 h. In poor metabolizers, the t1/2 of risperidone is extended to approximately 16 h. The active moiety is unchanged even in the presence of poor metabolizers. Renal clearance of risperidone is reduced in patients with impaired renal function (5). The therapeutic dose range is 3–8 mg, twice daily, which may need to be reduced in special patient groups (elderly and renal diseased) (4).

Case History

A 45-year-old male was reported missing one day prior to being found deceased at a local lakeside park. The missing persons report filed with the local police department stated that the male had a prior history of schizophrenia and previous suicide attempts. The missing male had attempted suicide 4 years previously by slashing his throat and more recently by taking an overdose of medications.

At the time the decedent was found, he was fully clothed, and he showed no visible signs of trauma. Three empty prescription vials of risperidone were found with the body. The first bottle was for 186 1-mg tablets and was filled 3 months prior to death; the second bottle was for 124 1-mg tablets and was filled 2 months prior to death; and the third bottle was for 93 1-mg tablets and was filled 1 month prior to death. These medications were prescribed by the local Mental Health and Mental Retardation clinic where he had been undergoing treatment. There was also an audiotape expressing “hopes for a better life” and “good-bye, I love you” to the family.
Experimental

Materials
Risperidone and 9-hydroxy-risperidone were supplied by Janssen Pharmaceutical, Inc. (Titusville, NJ).

Analysis
The method of detection was essentially that of Dong and DiCesare (6) with some modifications for our system. Samples and standards were alkalinized with saturated Na₂CO₃ and extracted with 2% isooamyl alcohol in hexane. The solvent was evaporated, and the residue was dissolved in the mobile phase. A Perkin-Elmer series 200 LC pump, a 235C diode-array detector at a wavelength of 280 nm, a silica column, and PE-Nelson software were used for analysis. The solvent was modified to CH₂CN-MeOH-iso-PrOH-NH₄OH (84:12:3:6:0.4) with a flow rate of 2 mL/min to allow an analysis time of 5 min. The solvent system was sufficient to resolve all drugs and the internal standard, imipramine. Sample peaks matched reference drug peaks for retention time and spectral characteristics.

Results
The autopsy findings were essentially unremarkable. An adherent small amount of frothy fluid was found in the oral cavity. The lungs were moderately congested, hyperinflated, and edematous. There was acute, diffuse visceral congestion, bilateral, moderate leptomeningeal congestion, and acute cerebral edema.

Routine laboratory analyses were negative for ethanol in blood, urine, and vitreous as were immunoassays for cocaine, opiates, and cannabinoids. These specimens were also negative for ethychlorvinol and salicylate. Buspirone and perphenazine were detected in the routine acid–base–neutral screen. Both drugs were extracted in the base screen using n-butyl chloride on the alkalinized samples followed by gas chromatography (GC) using nitrogen–phosphorus detection, and both were confirmed by GC–mass spectrometry (MS).

Risperidone and its 9-hydroxy metabolite proved to be more of a problem. Both of these compounds undergo thermal degradation in the gas chromatograph and were not detected in the routine screen; also, we were unable to determine any conditions that would allow us to confirm by GC–MS. The samples were analyzed and confirmed by high-performance liquid chromatography (HPLC) with diode-array detection.

Discussion
Brown et al. (2) reported an account of an overdose involving risperidone. The patient, a 29-year-old male, ingested 120 2-mg risperidone tablets in a suicide attempt 45 min before his arrival in the emergency department. On examination, the patient was alert and oriented to person, place, and time. The patient described auditory hallucinations but had no physical complaints. He exhibited some cardiac conduction disturbances that were self-resolving and an electrolyte imbalance, which was treated by an in-hospital regimen. After 24 h, the patient was discharged to the mental health center without any apparent untoward effects.

The present case report describes the only death reported in the literature. The laboratory findings were significant because the blood concentration of 1.8 mg/L (Table I) exceeded by 500-fold the normal therapeutic range of 0.00368 mg/L (based on a mean steady-state trough concentration of risperidone, 0.46 mg/L per 1-mg dose using a maximum of eight 1-mg doses per day) (4). These concentrations represent a relatively “pure” risperidone overdose despite the presence of buspirone at 0.05 mg/L. A single, 20-mg dose of buspirone yields a peak plasma concentration of 0.001–0.006 mg/L. In clinical pharmacology trials, doses as high as 375 mg/day were given to healthy male volunteers, and they experienced only minor side effects (7). The buspirone concentration was well below significant toxic levels and would probably have little consequence toward potentiation of risperidone.

Consideration to detection will have to be given to this drug because of thermal degradation in the gas chromatograph. It will not be detected in routine screens by GC or GC–MS. Case history, and inclusion into an HPLC screen, will be important.

Table I. Concentration of Risperidone, Buspirone, and Perphenazine in Postmortem Specimens

<table>
<thead>
<tr>
<th></th>
<th>Blood (mg/L)</th>
<th>Urine (mg/L)</th>
<th>Gastric contents (total) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>1.8</td>
<td>14.4</td>
<td>1.04</td>
</tr>
<tr>
<td>9-Hydroxy-risperidone</td>
<td>–</td>
<td>17.8</td>
<td>–</td>
</tr>
<tr>
<td>Buspirone</td>
<td>0.05</td>
<td>0.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>–</td>
<td>2.0</td>
<td>–</td>
</tr>
</tbody>
</table>

References

Manuscript received April 28, 1995; revision received August 1, 1995.