Abstract

The occurrence of zimelidine, a new experimental antidepressant, in a sudden death is presented. Tissues were extracted with n-butyl chloride. Quantitation was done by capillary gas chromatography with a nitrogen/phosphorus detector. Drug confirmation was obtained by gas chromatography and mass spectrometry. Blood concentrations of zimelidine and its metabolite norzimelidine were 0.71 and 2.2 mg/L respectively. Concentrations of the drug and metabolite are also given for the urine, liver, bile, and brain.

Introduction

In recent years, the search for the "perfect" antidepressant has led to the introduction of many new drugs. Recently, in the author's laboratory, a case involving the use of zimelidine was encountered.

Zimelidine, marketed as Zelmid by Astra Pharmaceuticals Ltd., is a new antidepressant which is presently used only experimentally in Canada but which has been available in Europe for several years. Zimelidine (Figure 1), a bicyclic derivative of the antihistamine pheniramine is structurally unrelated to the tricyclic and tetracyclic antidepressants. It is a relatively specific inhibitor of the reuptake of serotonin in central neurons (1).

Case History

A 30-year-old female who was receiving psychiatric care died as a result of a self-inflicted gunshot wound. Her known medication was zimelidine—100 milligrams twice daily, methyprylon, oxazepam, and tetracycline. Tissues received after autopsy were: blood, urine, liver, bile, and brain.

Experimental

Materials

Zimelidine, norzimelidine, and the internal standard CPP-235 [(Z)-3-(4-bromophenyl)-N-propyl-3-(3-pyridyl)-allylamine oxalate] were provided by Astra Pharmaceuticals Canada, Ltd., and n-butyl chloride was reagent grade from Caledon Laboratories Ltd.

Extraction

The optimum extraction (60%) of zimelidine and its metabolite was achieved using n-butyl chloride. Blood standards were spiked with zimelidine and norzimelidine in concentrations ranging from 0.10 to 1.0 mg/L. To a 2.5 mL blood sample, 0.1 mL of the internal standard (25 mg/L CPP-235) was added and the sample basified with 0.1 mL concentrated NH₄OH prior to extraction with 10 mL n-butyl chloride. The samples were shaken for 5 min and then centrifuged. The n-butyl chloride extract was then back-extracted with 1.0 mL 0.1 N H₂SO₄. Use of a stronger acid at this step resulted in a significant loss of norzimelidine. The organic layer containing the methyprylon was evaporated and reconstituted in ethanol for quantification. In addition to zimelidine and norzimelidine, this fraction was also used for quantification of diphenhydramine using promethazine as the internal standard.

A similar extraction was performed with 2.5 mL urine, 2.5 mL liver/water homogenate (1/1), 2.5 mL brain/water homogenate (1/1), and 2.5 mL bile.

To determine total bile zimelidine and norzimelidine concentrations, 2.5 mL bile and 0.1 mL CPP-235 were hydrolyzed with 2.5 mL 1.0 N H₂SO₄ in a pressure cooker for 20 minutes. Spiked aqueous standards were treated similarly. The filtered hydrolysates were extracted with 10 mL n-butyl chloride. The aqueous...
fractions were basified with 1.0 mL 4N NaOH and extracted with 10 mL n-butyl chloride. After centrifugation the organic layer was removed and evaporated.

**Instrumental Data**
Gas chromatography was performed on an HP 5880A instrument with a nitrogen/phosphorus detector. A 15-m DB-1 fused silica capillary column was programmed from 160°C to 280°C increasing at 8°C per minute. The helium carrier gas flow was 2 mL/min. Retention times for diphenhydramine, zimelidine, norzimelidine, promethazine, and CPP-235 were 4.13, 7.55, 7.73, 8.05, and 9.32 min, respectively. A typical gas chromatogram of a blood extract is shown in Figure 2.

Mass spectra were obtained on a 4500 Finnigan electron impact mass spectrometer. The mass spectrum of zimelidine has a base peak of 58 and a molecular ion of 316. The bromine isotope cluster accounts for the peak at 318 (Figure 3). Norzimelidine has a base peak of 147 and a molecular ion of 302 (Figure 4).

**Results and Discussions**
The drugs found in this case in addition to zimelidine and norzimelidine were diphenhydramine and methyprylon (Table 1). The blood zimelidine and norzimelidine levels were 0.71 and 2.2 mg/L, respectively. Normal, therapeutic plasma concentrations of zimelidine range from 0.02 to 0.25 mg/L (1,4-9). However, as with tricyclic antidepressants, individual variations do occur with zimelidine concentrations with steady-state plasma levels having been reported up to 0.8 mg/L (4,8). There is very little information in the literature on overdosage of zimelidine. One case of a woman who took 35 tablets (50 mg each) and survived has been reported (10). The zimelidine level 12 hours after the overdose was 0.6 mg/L.

Reported therapeutic norzimelidine levels are 2 to 4 times those of zimelidine (4-9), which is consistent with this case. However, in the liver the ratio of norzimelidine to zimelidine was 1 to 3. This contrasts to a 4 to 1 ratio found in the liver of a drowning victim whose blood zimelidine and norzimelidine concentrations were 0.3 and 0.9 mg/L respectively (11).

Norzimelidine was excreted more extensively in the urine than was zimelidine. Blood and brain concentrations were of the same order.

The concentration of non-conjugated norzimelidine in the bile was 3.7 times that of zimelidine. This compares to a 3 fold difference found in the drowning victim reported previously (11). In this case, the ratio of conjugated to free in bile was 2 to 1 for both zimelidine and norzimelidine.

This paper has reported zimelidine and norzimelidine levels in a suicide victim. It must be emphasized, however, that in this case death was not due to an overdose but normal therapeutic concentrations have been exceeded.
Table I. Summary of Toxicology Findings

<table>
<thead>
<tr>
<th>Drug</th>
<th>Blood mg/L</th>
<th>Liver mg/kg</th>
<th>Urine mg/L</th>
<th>Brain mg/kg</th>
<th>Free mg/L</th>
<th>Total mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimelidine</td>
<td>0.71</td>
<td>24</td>
<td>1.5</td>
<td>0.77</td>
<td>1.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Norzimelidine</td>
<td>2.2</td>
<td>8.2</td>
<td>11</td>
<td>3.7</td>
<td>5.2</td>
<td>16</td>
</tr>
<tr>
<td>Diphenydramine</td>
<td>0.30</td>
<td>0.77</td>
<td>3.8</td>
<td>0.37</td>
<td>1.9</td>
<td>—</td>
</tr>
<tr>
<td>Methyprylon</td>
<td>14</td>
<td>41</td>
<td>100</td>
<td>12</td>
<td>17</td>
<td>—</td>
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References


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