Tranylcypromine Concentrations and Monoamine Oxidase Activity in Tissues from a Fatal Poisoning

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Abstract

The case of a 55-year-old woman who died following the ingestion of 300 mg of tranylcypromine and several other drugs is presented. High concentrations of tranylcypromine were found in blood, brain, liver, and urine by gas-liquid chromatography. Monoamine oxidase activity in liver was markedly diminished from that of the control case, although the cerebral cortical activity of this enzyme did not differ significantly from the control. Pathological findings were limited to pulmonary edema and congestion of the liver, spleen, and kidneys.

Introduction

Tranylcypromine, or phenylcyclopropylamine (Figure 1), is currently marketed in the United States as an antidepressant agent. Its psychological effects are apparently due to its ability to inhibit cerebral monoamine oxidase (MAO), thereby increasing biogenic amine levels. The compound was temporarily withdrawn from the United States market in 1964 following a series of reports on its clinical toxicity (1). Hypertensive crises, occasionally fatal, have occurred in patients receiving therapeutic dosages (10-30 mg daily). Toxic reactions are more likely to result if the drug is coadministered with other MAO inhibitors or sympathomimetic agents. Tranylcypromine may also potentiate the effects of certain central nervous system depressants (2).

![Diagram of chemical structures]

Previously reported fatal cases of intentional overdose of tranylcypromine have involved 130-850 mg of drug, with or without the presence of other therapeutic agents (3-7). Rarely, however, are toxicological findings given and none of these reports have included fatal blood concentrations of the drug.

We report here the case of a 55-year-old woman who died after allegedly ingesting 300 mg of tranylcypromine and several other drugs. The complete toxicological and pathological findings are included with the results of a study of the monoamine oxidase activity in the brain and liver of the victim.

Case Findings

History: A 55-year-old white female with several past suicide attempts was brought to the hospital emergency room in a somnolent condition. On questioning she admitted consuming 30 Parnate (tranylcypromine, 10 mg) tablets, 30 Drixoral (d-brompheniramine, 6 mg and d-isoephedrine, 120 mg), and an unknown amount of propoxyphene and alcohol. Stomach lavage was performed and fluids were administered intravenously to stimulate diuresis. She was transferred to the intensive care unit, where over the next 3 hours she became cyanotic and hypotensive and developed respiratory difficulty. Resuscitation efforts included tracheal intubation and intravenous administration of dopamine and isoproterenol. Death was pronounced approximately 3 hours after admission.

Pathological Findings: The autopsy disclosed cardiac hypertrophy with focal atherosclerosis of the coronary arteries. Both lungs were diffusely edematous with congestion and edema and focal atelectasis in the lower lobes. There was congestion of the liver, spleen, and kidneys. Microscopic sections of the brain showed minimal focal anoxic changes.

Toxicological Findings: Samples of blood, brain, liver and urine were submitted for toxicological analysis. Screening of the samples for alcohol and for acid and neutral drugs by gas chromatography yielded negative results. Tranylcypromine, d-brompheniramine and d-isoephedrine were quantitated in the specimens using a gas chromatographic procedure developed for amphetamine analysis (8), which utilizes N-propylamphetamine as internal standard. Propoxyphene and its metabolite were analyzed by a separate gas chromatographic method (9). The quantitative results are shown in Table I.

Samples of brain and liver were evaluated for their monoamine oxidase activity following the method of Wurtman and Axelrod (10). Autopsy tissues of both the reference case (tranylcypromine overdose) and a control case (propropoxyphene overdose) for purposes of the MAO assay had been stored for 2 days following autopsy in glass jars at 4°C. Representative portions of these tissues were selected and frozen at -70°C for an additional 2 weeks until the MAO assay was performed. Tissue was homogenized in 10 volumes of 0.05M phosphate buffer, pH 7.2, and the homogenate was centrifuged for 10 min at 1000 xg. Triplicate samples of the supernatant containing approximately 0.5 mg of protein were used for the MAO assay.

The MAO assay used [14C]-tryptamine as substrate (final concentration, 1.6 x 10^-5 M) and enzyme activity was expressed as mmoles of product (indoleacetic acid) formed per ng
of Lowry protein per hour. Boiling of the supernatants at 100°C for 10 min prior to adding the radioactive substrate served as the enzyme blanks for the assay.

Compared to the propoxyphene overdose, there was a significant (p<0.001) reduction in the MAO activity in the right lobe of the liver of the tranylcypromine overdose (Table II). No significant difference was observed in MAO activity of cerebral cortical tissue when tissues from these two autopsy cases were compared (Table II).

### Table I. Concentrations of Drugs Found in Autopsy Specimens (μg/ml or μg/g)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Tranylcypromine</th>
<th>d-Isosephedrine</th>
<th>d-Brompheniramine</th>
<th>Propoxyphene</th>
<th>Norpropoxyphene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>3.7</td>
<td>11</td>
<td>0.2</td>
<td>1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Brain</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>7.3</td>
<td>11</td>
<td>4.5</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Urine</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table II. Monoamine Oxidase Activity of Post-Mortem Tissue Specimens (μmoles product formed 1mg protein/h)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Control Case</th>
<th>Tranylcypromine Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortex</td>
<td>3.39 ± 0.18</td>
<td>3.02 ± 0.26**</td>
</tr>
<tr>
<td>Right lobe of liver</td>
<td>11.24 ± 0.14</td>
<td>2.34 ± 0.29***</td>
</tr>
</tbody>
</table>

** Average of 3 separate determinations

*** P < 0.001 vs control

### Discussion

The pathological findings in this case were relatively non-specific. Some tranylcypromine fatalities have given evidence of cerebral hemorrhage, indicative of hypertensive crisis (7,11); other cases have been reported in which this was not a prominent finding (4,11). Hyperthermia, generalized tremor associated with hyperactivity, and hypertension or hypotension leading to circulatory collapse are signs of tranylcypromine toxicity (2-6) which are characteristic of the sympathomimetic agents as a class (12).

The concomitant use of d-isosephedrine in this case may have played a significant role in the death, as other sympathomimetic agents are especially contraindicated during tranylcypromine therapy (2). Plasma ephedrine concentrations resulting from therapeutic administration are generally less than 0.1 μg/ml (13) as compared to the 11 μg/ml observed in this case (Table I).

The tissue concentrations of tranylcypromine and especially the blood concentration are suggestive of massive overdosage with this drug. While therapeutic blood concentrations of tranylcypromine generally fall into the range of 10-100 ng/ml (14), there is no data of which we are aware regarding toxic concentrations. The two studies (7,11) which did present toxicological data reported liver concentrations of 0.5 and 1 μg/g and a urine concentration of 3 μg/ml. One of these cases involved the ingestion of 850 mg of drug (7) while the dosage in the second case is unclear (11).

The effects of coadministration of propoxyphene, a narcotic analgesic, in the present case are difficult to predict. The concentrations of propoxyphene and norpropoxyphene found in the tissues (Table I) are indicative of moderate but not severe overdosage. Therapeutic usage of this drug may result in plasma concentrations as high as 0.75 μg/ml (13), whereas toxicity is generally manifested at concentrations exceeding the 1.0 μg/ml observed in this case (15).

As tranylcypromine is commonly thought to exert its pharmacological effects primarily by inhibition of MAO, it was of interest to establish the activity of this enzyme in the tissues of the victim. Comparable sections of tissue were taken from another suicide case which involved similar circumstances but was attributable solely to propoxyphene.

The time during which a body remains at room temperature after death may influence the MAO activity. In studies on rat brain obtained post mortem MAO activity was found to be stable for 120 hours at 5°C and for 4 hours at 33°C (16). Recent studies on MAO activity in suicides concluded that the time interval between death and autopsy (between five and 148 hours) was not a major factor in the MAO activity found (17). Since our cases were matched for postmortem time, propoxyphene overdose would appear to be a valid control.

In the present study MAO activity was significantly reduced in the liver of the reference case (case 1) as compared to the "control case" (case 2). The lack of significant difference in MAO activity in the cerebral cortex of these two cases might be related to the distribution of the drug. In tissue from the corpus striatum (caudate) from case 1 the radioactive product of the MAO assay was not above the boiled blank values. This indicates vanishingly low activity of MAO in this brain region which is reported to have similar MAO activity as the cerebral cortex (16). However, since a matched sample of striatal tissue from the control case (case 2) was not obtained, an unequivocal statement as to differences in brain distribution of the tranylcypromine (MAO inhibitor) in case 1 cannot be made.

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### References