One Fatal and One Nonfatal Intoxication with Tranylcypromine. Absence of Amphetamines as Metabolites

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Abstract

Two very different cases of overdose with tranylcypromine are presented. One clinical case involving the ingestion of 400 mg tranylcypromine with suicidal intention and one fatality with a suspicion of possible tranylcypromine overdose were examined. Both cases showed similar blood concentrations (0.5 and 0.7 mg/L, respectively), but the clinical case exhibited only mild symptoms of intoxication. The fatality showed no other drugs that could provide an explanation for the death of a 40-year-old male except tranylcypromine. Consideration of the drug concentrations in the fatality in relation to the case findings and other reported data indicates the tranylcypromine overdose as the probable cause of death, despite the low blood concentration. In addition, we looked for evidence of amphetamine as a putative metabolite in both cases. No amphetamines were detected in the overdose cases reported here.

Introduction

Tranylcypromine is a monoamine oxidase (MAO) inhibitor that is commonly used in the treatment of depression, especially in patients who do not respond to other antidepressants. The irreversible inhibition of monoamine degradation is responsible for the antidepressive effect, but it can also cause interaction with sympathomimetics or with tyramine from food. Symptoms of interaction or overdose are hypertensive crisis, hyperreflexia, shock, and convulsions (1-4). The metabolic conversion of tranylcypromine to amphetamine has been proposed by Youdhim et al. (5). This is a possible explanation for symptoms in cases of overdose or reports of tranylcypromine abuse (6). On the other hand, Riederer et al. (7) could not detect any amphetamines at therapeutic dosage of tranylcypromine. Although suicide with antidepressants occurs quite often, only three reports (8-10) gave blood concentrations of tranylcypromine. We report here on toxicological data of one fatal and one nonfatal case of tranylcypromine overdose. In addition, we investigated whether the potential metabolites of tranylcypromine, amphetamine or methamphetamine could be found.

Materials

Tranylcypromine sulfate racemate was donated by Procter & Gamble (Weiterstadt, Germany). Methyleneoxyamphetamine (MDMA) and amphetamine-d3, which were used as internal standards, were obtained from Sigma (Deisenhofen, Germany). Hepafluorobutyric anhydride (HFBA) was purchased from Fluka (Buchs, Switzerland). All other chemicals and reagents were of analytical grade and were used as purchased.

Methods

Systematic toxicological analysis

Urine samples were screened for basic drugs and drugs of abuse by immunoassay using the Syva ETS (Darmstadt, Germany) and Abbott ADx (Wiesbaden-Delkenheim, Germany) systems according to the manufacturers instructions. Further screening for “general unknown” drugs was performed after alkaline or acid liquid-liquid or solid-phase extraction (SPE) using thin-layer chromatography (TLC) (11), GC, gas chromatography–mass spectrometry (GC–MS) (12), and high-performance liquid chromatography (HPLC) (13).

Ethanol was determined in blood and urine samples by GC–flame-ionization detection (FID) using a column packed with 0.2% Carbowax 1500 on a 60/80 mesh Graphpac (Restek, Bad Soden, Germany).

Determination of tranylcypromine

Blood and urine samples were diluted with an equal amount of water; solid-tissue samples were minced and homogenized with twice as much water. After dilution, blood and solid samples were ultrasonicated for 30 min, then centrifuged. The supernatant was extracted according to the method that Cody and Schwarzhoff (14) used for the determination of amphetamines in urine. The samples were extracted at pH 11 with 1-chlorobutane. The organic phase was re-extracted with 0.15M H2SO4. The aqueous phase was transferred, adjusted to pH 11, and extracted again with 1-chlorobutane. Isopropanolic HCl (200 μL; Merck, Darmstadt, Germany) was added to the
Table I. Toxicological Data of Blood Concentrations Following Fatal and Nonfatal Tranylcypromine Overdose

<table>
<thead>
<tr>
<th>Tranylcypromine concentration (mg/L)</th>
<th>Outcome</th>
<th>Dose (mg)</th>
<th>Circumstances</th>
<th>Other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1 Blood, 0.5</td>
<td>Survival; pulse 115/min; no severe symptoms</td>
<td>400</td>
<td>gastric lavage 3 h after ingestion</td>
<td>Not detected</td>
</tr>
<tr>
<td>Urine, 2.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 2 Blood, 0.7</td>
<td>Death; survival time unknown</td>
<td>400-700</td>
<td>unknown</td>
<td>BAC*, 0 mg/dL</td>
</tr>
<tr>
<td>Liver, 1.9</td>
<td></td>
<td></td>
<td></td>
<td>UAC, 150 mg/dL</td>
</tr>
<tr>
<td>Urine, 238.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference 5 Plasma, 0.93</td>
<td>Survival; pulse 120/min; BP 140/100; confusion, dilated pupils</td>
<td>250</td>
<td>admission to hospital 22 h after ingestion; Diazepam and Chlorpromazine were administered</td>
<td>not detected</td>
</tr>
<tr>
<td>Reference 8 Heart blood, 5.0</td>
<td>Death; survival time 6 h</td>
<td>unknown</td>
<td>unknown</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Iliac blood, 9.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver, 21.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference 8 Blood, 1.7</td>
<td>Death; survival time 48 h</td>
<td>unknown</td>
<td>unknown</td>
<td>not detected</td>
</tr>
<tr>
<td>Urine, 50.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference 9 Blood, 3.7</td>
<td>Death; survival time unknown</td>
<td>300</td>
<td>unknown</td>
<td>Dextropropoxyphene d-Isophephedrine</td>
</tr>
<tr>
<td>Urine, 25.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference 10 Blood, 0.25</td>
<td>Death; survival time unknown</td>
<td>850</td>
<td>unknown</td>
<td>not detected</td>
</tr>
<tr>
<td>Liver, 13.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: BAC = blood alcohol concentration; UAC = urine alcohol concentration; BP = blood pressure.

![Chemical structures](image_url)

Figure 1. Chemical structures of tranylcypromine, N-acetyltranylcypromine, amphetamine, and selegine.

Calibration curve

Calibration curves for tranylcypromine, amphetamine, and methamphetamine were determined with 1 mg/L MDMA or amphetamine-d₃ as internal standard. The ratios of the peak areas of amphetamine, methamphetamine, and tranylcypromine to MDMA or amphetamine-d₃ were used to calculate the concentration of the analytes in specimens. Standard calibration curves were linear over the range of 0.1 to 100 mg/L. The limit of quantitation was approximately 0.06 mg/L for tranylcypromine and 0.02 mg/L for amphetamine and methamphetamine. Both internal standards were used alternately to ensure that possibly detected traces of amphetamine did not result from degradation or contamination of amphetamine-d₃.

Case Reports

Case 1

A 35-year-old male took 40 10-mg tranylcypromine tablets with the intention of committing suicide. Approximately 3 h after ingestion he was taken to the hospital where gastric lavage was performed immediately. He developed mild tachycardia (115 beats/min) and was sweating profusely. The patient was discharged the next day without any toxic symptoms. Directly after gastric lavage, tranylcypromine concentration was determined to be 0.51 mg/L in plasma and 2.4 mg/L in urine.

Case 2

A man known to be addicted to alcohol and different drugs...
and with a history of several suicide attempts in the past was found dead in his bed. An empty box of 100 tranylcypromine tablets and several alcoholic beverages were found near the decedent. The tablets had been prescribed by his doctor two weeks previously and were to be taken twice per day. The determined tranylcypromine concentrations are shown in Table I and compared with the data from Case 1 and other reported data from fatal and nonfatal overdose cases.

Postmortem findings were as follows: the stomach was completely empty; the bladder contained 300 mL urine; the liver showed a fatty degeneration due to known chronic alcohol abuse; lung and brain tissue were oedematous and congested; and the heart, coronary vessels, and aorta did not show any pathologic changes.

Results and Discussion

The cases show comparable blood concentrations but a completely different outcome. The tranylcypromine concentrations in our cases are between those previously reported for therapeutic doses (i.e., 0.6 to 0.12 mg/L) (15,16) and the few other fatalities with documented blood levels of tranylcypromine (Table I). For this reason, it was not clear if a tranylcypromine overdose was the actual cause of death. One possible explanation is the low levels might be attributable to postmortem degradation of tranylcypromine as described by Yonemitsu et al. (17). They showed that blood samples spiked with tranylcypromine and incubated at 37°C for 48 h showed a 58% decline in tranylcypromine blood concentration. In a case of combined tranylcypromine and lithium overdose, the authors took blood samples from peripheral and central vessels at 0, 6, 24, 48, and 72 h after starting the autopsy. Blood concentration of tranylcypromine increased slightly during the first 24 h (1.3–1.6-fold), which was interpreted as a mild redistribution effect (Vd = 1.11–5.68 L/kg), whereas the concentration decreased within the next 48 h to levels that were much lower (25–80%) than those at the beginning. The decline was less pronounced in urine.

However, the time after death was at least 48 h in this case, so degradation effects might have contributed to the low tranylcypromine concentration.

Tranylcypromine is readily absorbed from the gastrointestinal tract and is rapidly eliminated (t1/2, 1.5 h) (15). The MAO-inhibiting effect of tranylcypromine is irreversible and therefore lasts considerably longer than blood concentrations of tranylcypromine can be determined. The extremely high tranylcypromine concentration of the nearly neutral urine (pH 6.8) in Case 2 and the alcohol concentrations in blood (0 mg/dL) and urine (150 mg/dL) point to a long time of survival. Boniface (8) reported one case with a survival time of 48 h (Table I), and Griffiths (18) reported a case with a survival time of 19 h but did not include tranylcypromine blood concentrations.

We also investigated whether amphetamines could be detected in these two cases of
overdose. Considering the increase in abuse of amphetamine and amphetamine derivatives, it is important to know which therapeutic drugs form amphetamines as metabolites. One example is the selective MAO B-inhibitor selegeline, which can easily undergo sequential oxidative N-desalkylation and yield R-(−)-methamphetamine and R-(−)-amphetamine (19) (Figure 1).

Although both cases of overdose reported here showed positive immunological results for amphetamines (cross-reactivity of tranylcypromine was approximately 1%), neither amphetamine, methamphetamine, nor other amphetamine derivatives could be detected (Figure 2). This is in accordance with Riederer et al. (7) and Spahn-Langguth et al. (20). Only Youdhim et al. (5) detected high concentration of amphetamine and methamphetamine in a case of tranylcypromine overdose and postulated the metabolic formation of amphetamine from tranylcypromine by cleavage of the cyclopropyl ring. Furthermore, they showed the formation of methamphetamine, but not amphetamine, after incubation of rat liver homogenate together with tranylcypromine. However, this metabolic pathway seems to be rather unlikely because there is no report on N-methylation of amphetamine or tranylcypromine even at previous oxidation. Even in the case of pyrethroids with unsaturated side chains, the cyclopropyl ring can only be split by photochemical reaction (21). These arguments and our findings do not support the hypothesis that amphetamine or methamphetamine might be metabolites of tranylcypromine.

References