Clozapine Tissue Concentrations following an Apparent Suicidal Overdose of Clozaril®

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Abstract

Clozapine is a tricyclic dibenzodiazepine derivative that is classified as an “atypical” antipsychotic drug. A 25-year-old male was brought to a hospital emergency room following the ingestion of an estimated 20 100-mg tablets of clozapine. After several hours in the hospital, the patient died. The cause of death was listed as acute clozapine intoxication. It was also noted upon autopsy that the patient had an unusual eosinophilic myocarditis. The toxicological and pathological findings are presented in this report.

Introduction

Clozapine is a tricyclic dibenzodiazepine derivative that is classified as an “atypical” antipsychotic drug. Its mechanism of action is primarily via an interaction with dopamine receptors in the brain’s limbic area (1). Clozapine was made available in the United States market in February 1990 under the trade name Clozaril® (2) and has been on the European market since the 1970s under the trade name Lepoxin®. It is available in tablets of 25 and 100 mg for oral administration. Because of the risk of agranulocytosis and seizures associated with its use, clozapine is recommended only for those cases in which patients have failed to respond adequately to standard antipsychotic drugs (1).

Relatively few cases of death resulting from an overdose of clozapine have been reported. This report describes clozapine tissue concentrations and pathological findings following an apparent overdose of Clozaril.

Case History

A 25-year-old, 231-lb. male was brought to the emergency room of a local hospital at 11:45 p.m. by his family, who suspected an overdose of medication. The patient had unsuccessfully attempted suicide with an overdose of haloperidol four years prior. His psychiatrist had recently started him on a prescription of clozapine (Clozaril). It was estimated that the patient took 20 100-mg clozapine tablets at 8:30 p.m. that evening. He appeared agitated, confused, combative, uncooperative, and required restraints throughout the procedures in the emergency room. At 12:45 a.m., blood was obtained for hospital laboratory work. A gastric lavage was performed at 1:50 a.m. with 6 L of normal saline solution. Large amounts of pill fragments and undigested food were recovered following the lavage. At 2:05 a.m., the patient was observed to turn blue and have a cardiac arrest, at which time CPR was initiated until his expiration at 2:31 a.m.

An autopsy was performed on the decedent approximately eight hours after death. The cause of death listed by the pathologist was acute clozapine intoxication. With the exception of cardiomegaly (440 g) and left ventricular hypertrophy, the gross pathologic findings were nonspecific for, but consistent with, acute drug intoxication. The etiology of the cardiac enlargement was not apparent anatomically or by clinical history. The microscopic description of the myocardium is discussed in a later section of this paper.

Methods

Toxicological analyses were performed on the blood obtained at the hospital emergency room (antemortem blood), postmortem heart blood, urine, liver, and gastric contents. Clozapine was extracted from the tissues utilizing a modification of the procedure described by Foerster et al. (3). Briefly, the procedure involved using 0.2, 0.5, and 1.0 mL of antemortem and post-mortem blood, 1.0 and 2.0 mL of urine at a 1:10 (v/v) dilution; 0.1, 0.2, and 0.5 mL of a 20% (w/w) liver homogenate; and 0.1 and 0.2 mL of the gastric solution.

After the addition of three drops of concentrated NH₄OH, 200 µL of prazepam at 10 µg/µL was added to each specimen as an internal standard. After mixing, the samples were then mixed and centrifuged, and the gas chromatography (GC) analysis.

Quantitation of clozapine was performed by dual column gas chromatography using a modification of the procedure of Watts...
and Simonick (4). A Hewlett-Packard GC equipped with a nitrogen–phosphorus detector was used for analysis. Separation and quantitation involved dual fused-silica megabore capillary columns (DB-1, 15 m x 0.542 mm i.d. with a 1.5-μM film thickness and DB-17, 15 m x 0.545 mm i.d. with a 1.0-μM film thickness). The operating parameters consisted of an isothermal column temperature of 250°C with the injector and detector temperatures at 250°C and 300°C, respectively.

Gas chromatography/mass spectrometry (GC/MS) analysis was performed on a Hewlett-Packard 5890/5970 GC/MS equipped with a fused-silica capillary column (DB-1, 15 m x 0.25 mm, i.d.). The operating parameters consisted of a column temperature program at 150°C (2 min) to 290°C (5 min) at 15°C/min. The injector and detector temperatures were 250°C and 300°C, respectively. The data acquisition was in the scan mode with a mass range of 40 to 500 amu.

Results

The structures of the tricylic dibenzodiazepine clozapine and its N-demethylated metabolite, norclozapine, are presented in Figure 1. GC/MS analysis determined that the five most abundant ions and relative percentages for clozapine were 243 (100%), 256 (89%), 70 (56%), 192 (49%), and 42 (47%) with a molecular ion of 326 (12%). Norclozapine produced ions of 243 (100%), 244 (67%), 256 (44%), 192 (39%), and 245 (33%) with a molecular ion of 312 (31%).

Upon GC/NP analysis, the retention times for clozapine and norclozapine on the DB-1 column were 5.098 and 5.231 min with the internal standard, prazepam, eluting at 4.275 min. The retention times for clozapine and norclozapine on the DB-17 column were 6.410 and 7.007 min with prazepam eluting at 5.418 min.

The tissue concentrations for clozapine are presented in Table I. Antemortem and postmortem blood concentrations were 1.94 and 5.81 μg/mL, respectively, while the urine had 11.3 μg/mL. The liver had 42.9 μg/g of clozapine and the gastric contained a total of 6.5 mg. Norclozapine was detected in some tissues but not quantitated because we lacked a proper standard. The percentages of norclozapine relative to clozapine were determined based on the area of the responses for the drugs upon GC/NP analysis (Table I). Antemortem and postmortem blood contained norclozapine at 10.8% and 12.0%, respectively, while the urine had only 7.8% of norclozapine relative to clozapine. The liver norclozapine percentage was 52.6% while the gastric contents had no detectable amount of norclozapine.

Discussion

Clozapine undergoes N-demethylation to form the metabolite norclozapine. The identification of norclozapine in this case was primarily via the mass spectral data (Figure 2). Clozapine has a molecular ion of 326 amu while the spectrum for norclozapine had a molecular ion 14 mass units less, at 312 amu, indicating the loss of a methyl group. Both compounds had similar spectra including the typical chloride atom pattern seen with many benzodiazepine drugs.

Table II summarizes the sequence of events leading to the expiration of the decedent. As can be seen, approximately 20 100-mg tablets of Clozaril were ingested at 8:30 p.m. The clozapine concentration of the blood sample taken approximately 4 h later, at 12:45 a.m., was 1.94 μg/mL. The patient was given a gastric lavage 5 hours and 20 min after the ingestion and eventually died 6 h after taking the overdose of clozapine. The postmortem clozapine heart blood concentration was 5.81 μg/mL.

Following oral dosages of 100 mg twice daily, the average steady state peak plasma concentration of clozapine was 0.32 μg/mL (range: 0.10–0.77 μg/mL), occurring at an average of 2.5 h (range: 1–6 h) after dosing (1). One case of suicide has been reported in which the patient took 3 g of clozapine while 11 other individuals have survived ingestion of more than 4 g (5). Schuster et al. (1977) reported a case in which a patient that was admitted 4 h after the ingestion of 3 g of clozapine subsequently recovered and was released three days later. Vesterby et al. reported two deaths attributed, in part, to clozapine intoxication and reported a clozapine blood concentration of 4.5 μg/mL and a plasma clozapine concentration of 3.2 μg/mL. In the case in-

![Figure 1. Structures of clozapine and norclozapine.](image)

![Figure 2. Mass spectra of clozapine and norclozapine.](image)

Table I: Clozapine Tissue Concentrations following an Apparent Suicidal Overdose of Clozaril®

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antemortem blood (μg/mL)</th>
<th>Postmortem blood (μg/mL)</th>
<th>Liver (μg/g)</th>
<th>Urine (μg/mL)</th>
<th>Gastric (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>1.94 (10.8%)</td>
<td>5.81 (12.0%)</td>
<td>42.9</td>
<td>11.3</td>
<td>6.5 mg Total</td>
</tr>
<tr>
<td>Norclozapine</td>
<td>0.04 (2.1%)</td>
<td>0.08 (3.2%)</td>
<td>(52.6%)</td>
<td>(7.8%)</td>
<td>(0%)</td>
</tr>
</tbody>
</table>

*Values for norclozapine are the percentages of the area of response relative to the area of the response for clozapine upon GC/NP analysis.
volving the 4.5 µg/mL concentration, the death was attributed to an accidental overdose caused by drug accumulation, primarily because of a low concentration in the gastric contents (0.4 mg total clozapine). It was also noted by the authors that the decedent had severe acute myocarditis with diffuse infiltration by mononuclear cells, predominantly histiocytes, and some granulocytes.

The microscopic examination of the heart in the present case revealed the presence of a striking myocarditis. The process, in contrast to the case reported by Vesterby et al., was of an intense interstitial infiltrate of eosinophiles associated with macrophages and occasional polymorphonuclear leukocytes and plasma cells. The inflammation was often perivascular, but there was no evidence of vasculitis. Muscle necrosis was not a predominant finding, but it was definitely multifocally present. These findings raised the question of the decedent’s possible use of L-tryptophan, but no such history could be obtained from the decedent’s physician or mother.

A few reports from outside the United States have described myocarditis in patients receiving clozapine (8). The type of myocarditis is not clear in most cases and its relationship, if any, to clozapine remains unclear. In some cases, the diagnosis was made by electrocardiography only. None of the case reports revealed the presence of eosinophilic myocarditis although, interestingly, several patients did develop some degree of peripheral eosinophilia during the course of myocarditis.

Norclozapine was identified in all specimens analyzed except the gastric contents in the present case. The percentages of norclozapine, relative to clozapine, were similar in antemortem blood, postmortem blood, and urine (10.8, 12.0, and 7.8%, respectively). The liver had a substantially higher norclozapine percentage (52.6%). Clozapine is reported to be completely metabolized before excretion with only trace amounts of unchanged drug detected in the urine (1). The present case shows a consid-

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2030</td>
<td>Took medication (20 100-mg tablets)</td>
</tr>
<tr>
<td>2345</td>
<td>Arrived at hospital emergency room</td>
</tr>
<tr>
<td>0025</td>
<td>Placed in restraints. Attempted to topple gurney, uncooperative, agitated, and confused</td>
</tr>
<tr>
<td>0045</td>
<td>i.v. started; blood obtained for labwork</td>
</tr>
<tr>
<td>0150</td>
<td>Lavaged with 6 L normal saline solution. Return of large amounts of pill fragments and undigested food</td>
</tr>
<tr>
<td>0200</td>
<td>Patient continues to thrash</td>
</tr>
<tr>
<td>0205</td>
<td>Patient becomes unresponsive and without pulse</td>
</tr>
<tr>
<td>0209</td>
<td>CPR initiated</td>
</tr>
<tr>
<td>0231</td>
<td>Patient expired</td>
</tr>
</tbody>
</table>

Table II. Sequence of Events of an Apparent Overdose of Clozaril

The antemortem blood concentration of 1.94 µg/mL may well be a good indicator of a lethal concentration of clozapine. This concentration occurred approximately 4 h after the suspected overdose, which is within the time required for peak clozapine concentrations to be achieved. The postmortem blood concentration (5.81 µg/mL) was approximately three times the antemortem blood concentration. A gastric lavage was given approximately 1 h after the antemortem blood specimen was obtained. This would tend to minimize further absorption of clozapine from the stomach. Thus, with the time allowed for clozapine absorption before the first blood specimen was drawn (4 h) and the subsequent gastric lavage, the increase seen with the postmortem clozapine heart blood concentration may be the result of postmortem redistribution.

As previously mentioned, 11 individuals have survived following the ingestion of more than 4 g of Clozaril. The present case involves a relatively large man (231 lb.) who died after the ingestion of only 2 g of Clozaril and who also had severe myocarditis. Thus, although the quantity of clozapine ingested may be fatal in itself, it is also possible that the myocarditis could have compromised the decedent’s chance for survival.

References

8. Personal communication, Sandoz Pharmaceuticals Corporation, East Hanover, New Jersey.

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