Fatal Overdoses Associated with Quetiapine*

Loralie J. Langman†, Henry A. Kaliciak, and Sheila Carlyle
Provincial Toxicology Centre, Riverview Hospital, Coquitlam, British Columbia, Canada

Abstract

Quetiapine (Seroquel®) is an atypical antipsychotic drug belonging to a new chemical class, the benzothiazepine derivatives. We present three cases from the Provincial Toxicology Center of British Columbia, Canada in which suicidal overdose deaths were associated with quetiapine. The blood specimens were initially subjected to a thorough qualitative analysis. Basic drugs were screened for by liquid-liquid extraction followed by gas chromatography–nitrogen-phosphorus (GC-NPD) and gas chromatography–mass spectrometry–electron impact detection utilizing both in-house and commercial search libraries. Acidic and neutral drugs were screened for by liquid-liquid extraction followed by high-performance liquid chromatography–diode-array detection. Volatiles were assayed by gas chromatography–flame-ionization detection. Quetiapine was assayed in biological specimens by basic extraction with n-butyl chloride and derivatized with 50 μL of MTBSTFA and separation by GC–NPD. Linearity was observed up to 2.0 mg/L. Samples with concentrations exceeding the linearity were diluted. These cases were chosen for study because they were all deaths as a result of suicidal ingestion of drugs in which quetiapine was considered a significant factor. The concentrations of quetiapine in these cases are 6–16 times greater than the upper reported therapeutic range (0.1–1.0 μg/L). In case #1, the concentrations of quetiapine found were 7.20 mg/L (19 pmol/L) in blood and 0.93 mg/L (2.4 pmol/L) in vitreous fluid. In case #2, the concentrations of quetiapine found were 16 mg/L in blood (42 pmol/L), 120 mg/kg (310 pmol/kg) in liver, and 1.8 mg/L (4.6 pmol/L) in vitreous fluid. In case #3, the concentrations of quetiapine found in femoral blood was 5.90 mg/L (15 pmol/L). In all cases, drugs in addition to quetiapine were detected, but in cases #1 and #2, the cause of death was considered to be a quetiapine overdose and the other drugs were not considered to be contributory. Case #3 was considered a mixed drug overdose.

Introduction

Quetiapine (Seroquel, 2-[(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)-ethoxyl]-ethanol fumarate, 2:1, salt, Figure 1), a dibenzotheazepine derivative, is an atypical antipsychotic agent which interacts with a broad range of neurotransmitters (1,2). Its use was approved by the FDA in 1997 for use for the management of the manifestations of schizophrenia (1). Atypical antipsychotics are categorized based on three characteristics: fewer extrapyramidal side effects than typical antipsychotics; relief from both positive symptoms (hallucinations, delusions) and negative symptoms (flat affect, avolition); and absence of prolactin elevation (3).

As with other antipsychotic drugs, the exact mechanism of action of quetiapine is unknown. Quetiapine is an antagonist at multiple neurotransmitter receptors in the brain. It has been proposed that this drug’s antipsychotic activity is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5-HT2) antagonism (2). It also has a high affinity for α1-adrenergic and histamine receptors but low affinity for muscarinic receptors (4). In general, reported signs and symptoms of overdose were predicted by the known receptor pharmacology, the absence of extrapyramidal effects related to D2 binding, the prominence of orthostatic hypotension and tachycardia from α1-adrenergic receptor blockade, and somnolence from histamine blockade (5).

Quetiapine is well absorbed from the gastrointestinal tract and reaches peak plasma levels within 2 h after oral administration (1,6,7). The half-life of the drug in blood is approximately 6 h. Steady-state plasma concentrations are achieved within 2 days of regular drug therapy. The volume of distribution of quetiapine is 8–10 L/kg (8), and it is 83% bound to plasma proteins (1,7,8). Quetiapine is extensively metabolized by the liver to over 20 metabolites, with only 3% of the drug being excreted unchanged (1,7). The major routes of metabolism involve oxidation of the side chain, hydroxylation...
findings include extensive scarring of extremities due to pre-
released with a defunctioning ileostomy. A full autopsy was to the abdomen, which were treated, and she was subsequently recently been admitted to hospital for self-inflicted stab wounds of bipolar disorder and self-mutilation, and she was consid-
ed topiramate, bupropion, paroxetine, lorazepam, Endocet of N- and O-dealkylation (6). The in vivo metabolic profile has not been fully elucidated, but previous studies showed the major in vivo metabolites of quetiapine were quetiapine sulfoxide and the parent acid metabolite. However these metabolites did not exhibit antipsychotic activity (7). The 7-hydroxylation of quetiapine is thought to be partly mediated by CYP3A4, although CYP2D6 was shown to be involved as well (6). The 7-hydroxy-quetiapine and 7-hydroxy-N-desalkyl-quetiapine are active metabolites, but with relatively low concentrations in blood (7).

The usual starting dose is 25 mg b.i.d. titrated with increments of 25–50 mg b.i.d., as tolerated, to a target dose of 300 mg/day given b.i.d. within 4–7 days (1,9). Further dosage adjustment may be indicated depending on the clinical response and tolerance in the individual patient (1). Dosage adjustment should occur at intervals of not less than 2 days, as steady state for quetiapine would not be achieved for approximately 1–2 days in the typical patient (1). Clinical trials suggest that the usual effective dose will be in the range of 300–600 mg/day (1). However, some patients may require as little as 150 mg/day. The safety above 800 mg/day has not been evaluated (1). The most common and clinically significant side effects associated with quetiapine therapy include dizziness, orthostatic hypotension, somnolence, weight gain, dry mouth, and dyspepsia (1,10).

We present three cases of suicidal overdose associated with quetiapine, as determined by the British Columbia Coroner’s Service.

Case #1 history
A 56-year-old female was found deceased on the bedroom floor a few hours after a family dispute and 45 min after last being seen. The deceased’s medical history included long-standing bipolar disorder and severe obsessive-compulsive disorder. At the scene, her medications (alprazolam, clonazepam, loxapine, benzotropine) were well accounted for, but some of her husband’s medication, Seroquel (quetiapine), appeared to be missing. A full autopsy was performed approximately 32 h after death. Significant findings included evidence of organizing interstitial viral-type pneumonitis and old self-inflicted forearm scars. There was no evidence of underlying chronic lung disease or of an aspiration event. Specimens were collected for toxicological analysis.

Case #2 history
A 39-year-old female was discovered dead in her apartment. The deceased medical history included a long-standing history of bipolar disorder and self-mutilation, and she was considered a suicide risk. The medications found at the scene included topiramate, bupropion, paroxetine, lorazepam, Endocet® (acetaminophen and oxycodone), and quetiapine. She had recently been admitted to hospital for self-inflicted stab wounds to the abdomen, which were treated, and she was subsequently released with a defunctioning ileostomy. A full autopsy was performed approximately 4 days (104 h) after death. Significant findings include extensive scarring of extremities due to previous self-inflicted wounds and peritoneal adhesions and ileostomy from surgical management of stab wounds. A thick, white “chalk-like” material was present throughout the esophagus and stomach. Specimens were collected for toxicological analysis.

Case #3 history
A 48-year-old female was found dead in her bed. Her past medical history included fibromyalgia, spinal stenosis, neurogenic bladder, and schizophrenia. The medications found at the scene included naproxen, topiramate, Tecnal® (butalbital and salicylate) and/or Tecnal-C® (butalbital, salicylate, and codeine), and quetiapine. Earlier in the evening she had called the crisis hot line and indicated she was feeling suicidal, and a suicide note was found at the scene. No autopsy was performed. Specimens were collected approximately 24 h after death for toxicological analysis.

Material and Methods
All specimens were collected at the time of postmortem examination and stored at 4°C until time of analysis.

The blood specimens were initially subjected to a thorough qualitative analysis. Basic drugs were screened for by liquid–liquid extraction followed by gas chromatography–nitrogen-phosphorus (GC–NPD) and gas chromatography–mass spectrometry (GC–MS) electron impact detection utilizing both in-house and commercial search libraries. Acidic and neutral drugs were screened for by liquid–liquid extraction followed by high-performance liquid chromatography–diode-array detection (HPLC–DAD). Volatiles were assayed by gas chromatography–flame-ionization detection (GC–FID).

Quetiapine standard was obtained from AstraZeneca Canada, Inc. (Mississauga, ON, Canada), and hydroxytriazolam was obtained from Cerilliant Corporation (Round Rock, TX). All other solvents and chemicals were the best available commercial grade.

The assay for quetiapine in biological specimens was developed in our laboratory. Briefly, to each tube, 1 mL of sample, 50 μL of internal standard (4-hydroxytriazolam (0.01 mg/mL)), and 1 mL of saturated sodium carbonate solution (pH 12) were added and extracted into 6 mL n-butyl chloride. The extract was concentrated under nitrogen, reconstituted, derivatized with 50 μL of N-[tert-butyldimethyl-silyl] N-methytrifluoroacetamide (MTBSTFA), and heated at 60°C for 30 min; 1 mL was injected into an Agilent (Agilent Technologies Canada, Inc., Mississauga, ON, Canada) model 5890 GC coupled to an NPD using a 12-m Ultra-1 capillary column (0.2-mm i.d., 0.33-μm film thickness, Agilent). Derivatization improves the peak shape and decreases the retention time during chromatography. The initial temperature was 260°C and increased 10°C/min for 1 min, then 50°C/min until 300°C, and then held for 2 min. The peaks eluted at 3.05 min for quetiapine and 2.49 min for the hydroxytriazolam (Figure 2). The concentration was measured by comparison of peak-height ratios of quetiapine to that of hydroxytriazolam against a standard curve. A five-point standard
curve was used and the correlation coefficient was 0.991 (r² = 0.995) or greater. Linearity was observed from 0.010 mg/L (0.026 µmol/L) up to 2.0 mg/L (5.2 µmol/L). Samples with concentrations exceeding the linearity were diluted with drug free matrix or saline. The CV at 0.10 mg/L (0.26 µmol/L) was 11.5% (N = 41), and sample recovery was greater than 95% throughout the linear range. No other unidentified NPD active compounds were detected in any of the cases; therefore, the potential for interference peaks is low, and no formal interference studies were undertaken.

Results

Case #1

Qualitative analysis in central blood identified acetaminophen, carbamazepine, lorazepam, clonazepam, diphenhydramine, and quetiapine. The central blood concentration of acetaminophen was less than 10 mg/L, carbamazepine was 8.5 mg/L (36 µmol/L), lorazepam was 0.05 mg/L (0.16 µmol/L), and clonazepam was 0.027 mg/L (0.086 µmol/L). With the exception of the acetaminophen concentration, which is less than therapeutic (0.010–0.10 mg/L) it is less than the commonly accepted minimum lethal level of 8 mg/L (8). Elevated concentrations of quetiapine (Table I) were found in central blood 7.20 mg/L (19 µmol/L) and in vitreous fluid 0.93 mg/L (2.4 µmol/L). The cause of death was ascribed to solely quetiapine overdose.

Case #2

Qualitative analysis in atrial blood identified acetaminophen, bupropion, topiramate, oxycodone, paroxetine, and quetiapine. The atrial blood concentration of acetaminophen was 36 mg/L (0.24 mmol/L), bupropion was 0.08 mg/L (0.33 µmol/L), hydroxybupropion was 0.44 mg/L (1.7 µmol/L), topiramate was 3.6 mg/L (11 µmol/L), oxycodone was 0.059 mg/L (0.19 µmol/L), and trace amounts of paroxetine were detected. With the exception of the topiramate concentration, which is less than therapeutic [5.9–35 mg/L (5)], the concentrations of oxycodone and bupropion are consistent with levels achieved therapeutically. The concentration of acetaminophen was 36 mg/L (0.24 mmol/L); neither the patient’s history, the autopsy finding (normal liver), nor the relatively low concentration of drug [minimum lethal level of 160 mg/L (8)] suggest that acetaminophen was contributory to the death. Elevated concentrations of quetiapine (Table I) were found in atrial blood 16 mg/L (42 µmol/L), liver 120 mg/kg (310 µmol/kg), and in vitreous fluid 1.8 mg/L (4.6 µmol/L). The esophageal/stomach content sediment was found to contain large quantities of quetiapine. The cause of death was ascribed to solely quetiapine overdose.

Case #3

Qualitative analysis in subclavian blood identified naproxen, topiramate, butalbital, salicylate, codeine, morphine, and quetiapine. The concentration in subclavian blood of naproxen was 130 mg/L (560 µmol/L), topiramate was 24 mg/L (71 µmol/L), butalbital was 11 mg/L (49 µmol/L), salicylate was 140 mg/L (0.99 mmol/L), codeine was 4 mg/L (13 µmol/L), and morphine was 0.087 mg/L (0.31 µmol/L). The concentrations of naproxen and topiramate are not beyond what could be achieved with therapeutic dosing (8). However, the concentrations of butalbital, salicylate, and codeine approach or exceed the minimum lethal levels (13 mg/L, 61 mg/L, and 1.0 mg/L respectively) (8). It was also noted that the concentrations of naproxen (Table I) found in femoral blood 5.90 mg/L (15 µmol/L) was significantly elevated above

Table I. Concentrations of Quetiapine in Body Fluids and Tissues

<table>
<thead>
<tr>
<th>Quetiapine mg/L or mg/kg (µmol/L or µmol/kg)</th>
<th>Blood</th>
<th>Vitreous fluid</th>
<th>Cause of death</th>
<th>Method of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case #</td>
<td>Central</td>
<td>Peripheral</td>
<td>Liver</td>
<td>0.93 (2.4)</td>
</tr>
<tr>
<td>2</td>
<td>16 (42)</td>
<td>120 (310)</td>
<td>1.8 (4.6)</td>
<td>Quetiapine overdose</td>
</tr>
<tr>
<td>3</td>
<td>5.9 (15)</td>
<td></td>
<td></td>
<td>Mixed drug overdose</td>
</tr>
</tbody>
</table>
the therapeutic range (0.1–1.0 mg/L) (11). There was insufficient volume of blood available to analyze the concentration of all the identified drugs in both subclavian and femoral samples. This death was considered a mixed drug overdose.

Discussion

During the time spanning 2000 to 2003, the Provincial Toxicology Center of British Columbia, Canada analyzed 7651 toxicology cases, and quetiapine was identified in 26 cases. Fifteen of those cases were ruled to be natural, accidental, or undetermined manner of death. The mean quetiapine concentration in these cases was 0.12 mg/L (0.31 µmol/L), and the median was 0.053 mg/L (0.14 µmol/L), with a range of 0.01 mg/L–0.65 mg/L (0.026–1.70 µmol/L). The remaining cases were classified as suicides where quetiapine was not implicated in the cause of death. The mean quetiapine in these cases was 0.19 mg/L (0.50 µmol/L), the median was 0.14 mg/L (0.37 µmol/L) with a range of 0.01 mg/L–0.74 mg/L (0.026–1.90 µmol/L). We present here three cases of suicidal overdose associated with quetiapine, as determined by the British Columbia Coroner’s Service. These cases were chosen for study because they were all deaths resulting from suicidal ingestion of drugs in which quetiapine was considered a significant factor. The concentrations of quetiapine in these cases are 6–16 times greater than the upper reported therapeutic range (0.1–1.0 mg/L) (11), assuming the blood/plasma ratio is 1:1. None of our cases were submitted with sufficient amounts of both central and peripheral blood samples, so an evaluation of the postmortem redistribution was not possible. In cases #1 and #2, only blood from the central compartment was submitted, and there were significant postmortem intervals ranging from 32 and 104 h, respectively. Given the large volume of distribution and high liver-to-blood concentration, an increase in central blood due to postmortem redistribution cannot be ruled out.

In case #1, clonazepam was detected. It has been reported that the concentration of clonazepam and its major metabolite 7-amino-clonazepam may be comparable in plasma with therapeutic dosing (8). Clonazepam appears stable in blood samples in the presence of sodium fluoride (8,12,13); however, in the absence of preservative, the concentration of clonazepam decreases and 7-amino-clonazepam increases in postmortem blood (13). Although the samples in case #1 had been stabilized with sodium fluoride at the time of autopsy, some deterioration of clonazepam may have occurred during the postmortem interval of 32 h. At the time the investigation of the case was undertaken, the 7-amino metabolite was not being quantitated, the clonazepam concentration was determined to be 0.027 mg/L (0.086 µmol/L) and within the ranges seen with therapeutic dosing (8,14). However, without the 7-amino-clonazepam concentration, a complete assessment of the contribution of clonazepam to the mechanism death may not be possible at this time.

In case #1, the vitreous fluid quetiapine concentrations was 13% (0.93 mg/L) of the blood concentrations (7.2 mg/L), and in case #2, the vitreous fluid concentration was 11% (1.8 mg/L) of the blood concentration (16 mg/L). Vitreous fluid is largely devoid of plasma protein and the quetiapine concentrations in this matrix would represent the portion that is not bound to plasma proteins. Our results are slightly lower, but still in keeping with what has been reported for non-protein bound fraction (17%) (1). In case #2, the liver concentration (120 mg/kg (310 µmol/L), was 7.5 times greater than the cardiac blood. This is potentially due to liver sequestering the drug for first pass metabolism and comparable to differences that have been previously described with concentrations in liver 2–8 times greater than that found in blood (15).

In case #3, the manner of death was clearly suicide due to a mixed drug overdose with co-ingestion of butalbital, salicylate, and codeine (probably Tecnal-C) and quetiapine. This latter case was included because quetiapine was probably contributing to death, but not the sole cause or principal agent causing death.

Concomitant ingestion of drugs that induce or inhibit CYP enzyme systems can affect normal metabolism of drugs and lead to adverse events and potential accidental overdose. In case #1, carbamazepine was identified as one of the concomitant medications and was detected at therapeutic levels. Use of quetiapine with CYP3A4 enzyme inducers, such as carbamazepine, increase the rate at which the drug is metabolized, thereby reducing the concentration of drug during a given time interval, and ultimately systemic exposure (1). It is unlikely the small amount of carbamazepine would have a significant impact on the large concentration of quetiapine found in this case. Coingestion of a CYP3A4 inhibitor could cause accumulation of quetiapine. In case #2, paroxetine was detected, although paroxetine has been reported to be CYP3A4 inhibitor, it is considered a weak inhibitor and unlikely to cause a problem at clinical concentrations (1). In case #2, the paroxetine levels were subtherapeutic and thought not to influence the quetiapine concentration, supporting the interpretation of suicide.

Quetiapine appears to have greater safety in overdose than traditional antipsychotic agents (5). Quetiapine overdose alone or in combination with other medications has resulted in QT prolongation (16), sinus tachycardia (17), and hypokalemia with first-degree heart block (1), orthostatic hypotension (1), and loss of consciousness (18). There are six reports of acute overdose in the clinical trial database (1). Doses ranged from 1200 mg to 9300 mg. No fatalities occurred and no information regarding concomitant ingestions was available for these six cases (1). Another case report (19) described an overdose of 4700 mg quetiapine with 600 mg fluoxetine taken by a 21-year-old man. The patient became disoriented and drowsy but did not lose consciousness. He also experienced sinus tachycardia at 128 bpm. At 4 h postingestion, the patient received gastric lavage and activated charcoal. He also required 4 mg of lorazepam intramuscularly for intermittent agitation. By 18 h postingestion, the patient was alert and oriented. However, he remained tachycardic for 48 h. In these reports, the patients recovered with supportive and symptomatic treatment. One case report suggests that in overdose situations there may be significant alterations to the pharmacokinetics of quetiapine (5). In this case a 40-year-old caucasian female with a

523
history of bipolar disorder, schizophrenia, and obsessive-compulsive disorder, allegedly ingested 3000 mg of quetiapine fumarate. She presented to the emergency department within 1 h of the ingestion and was found to be hypotensive with sinus tachycardia. There was evidence of nonspecific ST segment abnormalities, and PR and QT intervals were at the upper limit of normal. The patient received supportive treatment until stable. At 22 h, the physical and neurologic examination were essentially normal; however, the patient continued to have tachycardia until 42 h. Her serum quetiapine concentration 90 min after admission was 1.8 mg/L. This concentration is lower than predicted, and suggests that absorption is highly reduced, either by the effects of the overdose or by the activated charcoal she was administered. Serial quetiapine levels were analyzed, and quetiapine continued to be detectable until the seventh day after the overdose. Decline in serum quetiapine concentrations followed what appeared to be a biexponential pattern and suggested a terminal elimination half-life of 22 h in this patient (5). This is more consistent with previously noted duration of clinical effects and detectable serum concentrations after overdose than the published half-life of 6 h. Whether this is true of the drug at therapeutic dosing in the majority of patients is yet to be shown.

A case of an individual surviving with serum levels exceeding some of our cases has been reported. In this case, a 26-year-old female with a history of paranoid schizophrenia and multiple attempts of suicide, allegedly ingested greater than 10 g of quetiapine (17). At 1.25 h postingestion, the patient received gastric lavage followed by 50 g activated charcoal. The patient had a rapid loss of consciousness at 2.5 h postingestion and required intubation. At this time she also received naloxone. Signs and symptoms experienced by the patient included sinus tachycardia with a heart rate of 130–140, blood pressure of 135/70, and pupils 3 mm and sluggish. EKG and laboratory findings were all within normal limits. Within 16 h, the patient was awake and alert. Signs of tachycardia lasted for 40 h postingestion. The serum level was measured at 12.7 mg/L on admission. The patient was treated at the hospital, suffered no ill effects, and was transferred to a psychiatric hospital (17). It is assumed that the medical intervention had a significant effect on patient outcome.

A search of the literature produced three publications describing the detection, quantitation, and analysis of this drug in postmortem/perimortem specimens where drug overdose is the cause of death (11,15,20). In the paper by Anderson et al. (15), there were no cases described where overdose of quetiapine was considered the sole cause of death. The report by Mainland et al. (20) was of three cases of death associated with quetiapine. Two cases were ruled as mixed drug overdoses. The other case was ruled an accidental death due to quetiapine toxicity, and quetiapine was the only drug detected. The concentrations of quetiapine were 170 mg/L in cavity blood and 190 mg/kg in liver; 27 mg was found in the gastric contents. The significance of the very elevated cavity blood drug levels is difficult to interpret because of potential contamination from the liver and moderate state of decomposition reported in this case. The concentration in the liver is comparable to case #2 reported here where 120 mg/kg was detected. In the paper by Fernandes and Marcil (11), the serum concentration of quetiapine was 18.3 mg/L and exceeds the concentrations reported in our cases. The patient was reportedly taking felodipine, sertraline, busipiron, and haloperidol; however, the presence or absence of these drugs was not indicated in the report.

This report is the first to describe suicidal overdose cases where quetiapine is specifically implicated in the cause of death, and it reports the concentration of other medications detected postmortem. The literature revealed cases of individuals surviving with overdoses of quetiapine, some with concentrations greater than the cases reported here (1,5,16–19). However, it was assumed that medical intervention played an integral role in those patients’ recoveries. As was previously discussed, the quetiapine concentrations in the postmortem cases reported here were similar to those reported in other cases of overdose (11,15,20); however, from this small sampling, it is difficult to establish a minimum lethal level. What can be concluded is that quetiapine should be considered as a potential cause of death in the investigation of overdose cases when elevated levels of the drugs are detected, and that more investigation is needed.

Acknowledgments

Thanks to Dennis Friesen, Joan Morgan, and Rick White for their excellent technical assistance and to the British Colombia Coroner’s Service for permission to reference these cases.

References

12. M.D. Robertson and O.H. Drummer. Postmortem distribution and