Quetiapine in Overdosage

A Clinical and Pharmacokinetic Analysis of 14 Cases

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Abstract: Data on quetiapine overdosage are only sparsely available in the literature. This study provides additional data on the pharmacokinetics and clinical effects of intoxication with this atypical antipsychotic drug. The authors performed a retrospective analysis of all quetiapine intoxications reported to and screened by the toxicological laboratory of the Central Hospital Pharmacy The Hague between January 1999 and December 2003. Cases with known suggested amount of intake and medical outcome were included. From the patient's medical record and from the toxicological laboratory findings, patient demographic characteristics (gender, age), details of quetiapine intoxication (estimated time of ingestion, estimated amount of ingestion, and coingested drugs) and clinical parameters were obtained. Severity of intoxication was graded by the Poisoning Severity Score (PSS). Individual pharmacokinetic parameter values were calculated using a one-compartment open model and a Bayesian fitting procedure. Out of a total of 21 intoxications with quetiapine, 14 fulfilled the inclusion criteria. The ingested dose ranged from 1200 to 18,000 mg. The blood concentration ranged from 1.1 to 8.8 mg/L with a lag time of 1 to 26.2 hours between time of ingestion and blood sampling at the emergency ward. The most frequent findings were somnolence and tachycardia. The PSS was minor in 6 patients (43%), moderate in 5 patients (36%), and severe in 3 patients (21%). Severity of intoxication was not associated with a higher amount of quetiapine intake. The authors found no correlation between the serum concentration of quetiapine and the amount ingested. Elimination $t_{1/2}$ was not prolonged. It can be concluded that quetiapine intoxications appear to proceed mildly. Tachycardia and somnolence were the main clinical symptoms in our case series. No fatalities occurred. The severity of clinical symptoms was not associated with either a high serum concentration or the suggested amount ingested of quetiapine.

Key Words: quetiapine, intoxication, pharmacokinetics, PSS

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Quetiapine fumarate (Seroquel®) is an atypical antipsychotic drug that is indicated for the treatment of schizophrenia and the short-term treatment of acute manic episodes associated with bipolar I disorder. It belongs to the new class of dibenzothiazepine antipsychotics and is structurally similar to clozapine and olanzapine. Quetiapine has moderate affinity for serotonin ($5HT_{2A}$), adrenergic (α_1), muscarinic, and histaminergic receptors. It has only minor affinity for dopamine D_2 and $5HT_{1A}$ receptors and very low affinity for $5HT_{2C}$, α_2, and D_1 receptors.[1]

Quetiapine is thought to have fewer extrapyramidal symptoms, similar to clozapine, because of mixed $5HT_2$/D_2 binding and to have less anticholinergic and antiadrenergic effects than clozapine. Quetiapine is available in strengths ranging from 25 to 300 mg and has been shown to be effective over a broad dose range (up to 750 mg/d). Concentrations associated with efficacy are 0.02–0.3 mg/L.[2]

Adverse effects associated with quetiapine use can be explained by blockage of the α-adrenergic, muscarinic, and histamine receptors. Frequently observed adverse effects include tachycardia, hypotension, and somnolence.[1] Data on quetiapine in overdosage are only sparsely available in the literature.

Zbuk describes a case of a 40-year-old woman who became somnolent and developed tachycardia after ingestion of 3 g of quetiapine.[3] In 2 other case reports, self-limiting QTc-interval prolongation was associated with quetiapine overdosage.[4,5] To our knowledge, only 1 case of fatal overdage with quetiapine has been reported, after ingestion of 10.8 g.[6]

There is only 1 study that describes the clinical symptoms—eg, central nervous system depression and sinus tachycardia—that predict ICU admission and length of stay in hospital in 18 patients with a quetiapine intoxication. None of these patients had a fatal outcome.[7]

Knowledge of the clinical course of intoxication with certain drugs might assist in the decision-making process of whether or not to admit a patient to hospital.

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Apart from the clinical symptoms, knowledge on the pharmacokinetics of drugs in overdosage can play an important role in the treatment of the intoxicated patient.

However, few data on the clinical symptoms and the pharmacokinetics in patients suffering from quetiapine overdosage are available.[8] We conducted a retrospective study on the pharmacokinetics of quetiapine in relation to clinical symptoms in intoxicated patients, extracted from our toxicological database.

METHODS

Patients

The study design was retrospective and multicenter. All quetiapine exposures reported to the hospital pharmacy between January 1999 and December 2003 were included. All serum samples were screened by the toxicology laboratory of The Central Hospital Pharmacy, The Hague, serving 6 teaching hospitals in a population of approximately 750,000 people.

Cases were included if the intoxication was an intentional ingestion of an overdose of quetiapine. Cases were excluded if the suggested amount of intake and/or the medical outcome were unknown. From the patient's medical records and from the toxicology laboratory findings, patient demographic characteristics (gender, age), details of quetiapine intoxication (estimated time of ingestion, estimated amount of ingestion, and coingested drugs) were obtained.

Clinical Parameters

The patient's medical record was screened for the following clinical information: Glasgow Coma Scale on admission (GCS, expressed in EMV score), pupil size, cardiac investigations (pulse rate, blood pressure, QT interval and corrected QT interval [QTc interval]), respiratory stability, kidney function, hepatotoxicity, length of hospital stay, ICU admission, and medical intervention (drug administration, gastric lavage and laxation, respiratory and cardiovascular support) and medical outcome.

Intoxication severity was assessed according to the Poisoning Severity Score (PSS) of the European Association of Poison Centers and Clinical Toxicologists (EAPCCT).[9]

Minor symptoms included somnolence, tachycardia (100–140 ppm), hypotension (80–100 mm Hg), mild ECG changes, and mild rise of CPK (250–1500 U/L). Moderate symptoms included coma, tachycardia (> 140 ppm), hypotension (< 80 mm Hg), major rise of CPK (1500–10,000 U/L), and respiratory status (need for oxygen). Severe symptoms included coma and respiratory arrest. The poisoning severity of each patient was classified into minor, if only minor symptoms were present, into moderate if at least 1 moderate symptom had developed, and into severe if at least 1 severe symptom was observed.[9]

For each available ECG, the QT and the RR (interval between 2 complexes) were measured by an independent cardiologist using a magnifying reticule. QTc intervals were calculated using the Bazett formula. For patients with multiple ECGs, the first ECG after admission was used for analysis. The QTc interval was considered abnormal if longer than 440 milliseconds in men and 450 milliseconds in women.[10]

Analytic Techniques

Blood samples were screened with the I-tox® high-performance liquid chromatography toxicology screening system (Agilent, Amstelveen, The Netherlands), briefly described as follows: the patient's serum sample was mixed with prazepam as internal standard. After alkalization the compounds were extracted with dichloromethane, and the extract was evaporated to dryness. After solubilization in eluting solvent, an aliquot of 40 μL was injected onto a Merck Lichrosper RP-18 (5 μm) column (Merck, Darmstadt, Germany). The eluting solvent was 47% acetonitrile and 53% buffered solution, pH 3.3, and was run at 0.6 mL/min.

Eluting compounds were identified with the I-tox® drug library by matching the ultraviolet spectrum of each eluting compound to a library spectrum. A similarity of at least 0.995 was required for a positive identification. Quantification was carried out by measuring the absorbance at 210 nm. The limit of quantification for quetiapine was 0.01 mg/L. Toxicity of quetiapine was defined as a serum concentration above 0.5 mg/L.[11] With the I-tox® system, over 700 coingested drugs can be identified and quantified within the same analytic run.

Pharmacokinetic Analysis

Individual pharmacokinetic parameter values were calculated using a 1-compartment open model and a Bayesian fitting procedure (Mw/Pharm 3.50, Mediware, Groningen, The Netherlands[12]). The apparent absolute volume of distribution (V_d; L), the relative volume of distribution (V_d; L/kg), the absolute clearance (CL; L/h), the relative clearance (CL; L/kg/h), and the elimination half-life ($t_{1/2}$; h) for each individual patient were calculated, as well as population means (± standard deviation, SD), based on a pharmacokinetic model published earlier with volume of distribution (V_d) and elimination rate constant (K_{el}) as "a priori" estimates.[2] The suggested amount of ingestion, date of ingestion, suspected time point of ingestion, and measured serum quetiapine concentrations for each patient were imported into this pharmacokinetic model. Verification of the ingested amount of quetiapine, as mentioned by the patient or the nursing personnel in the emergency room, was performed by extrapolating the lag time and serum concentration through fitting the population model to the patient's data.

Elimination half-life ($t_{1/2}$; h) was extracted from the patient's data if at least 2 or more serum concentrations per patient were known. Elimination half-life was considered prolonged if it exceeded 6 hours (the population half-life[2]).

Statistical Analysis

All statistical tests were performed using SPSS Statistical Package for Windows, version 11.0 (SPSS, Chicago, IL).

RESULTS

Patients and Clinical Parameters

During the study period, 21 reports of patients with quetiapine poisoning were received from the emergency rooms of the participating hospitals. Seven cases were excluded from the study because the ingested dose was not known (6 cases) or loss of medical records (1 case).

The remaining 14 cases included 6 female and 3 male patients, of whom 2 women were intoxicated more than once with different doses.

All patients included were treated with quetiapine by a psychiatrist and intentionally took an overdose of the drug.

The median age of the patients was 32 years (range 20–54 years). The ingested dose ranged from 1200 to 18,000 mg with a median of 2600 mg (Table 1). The median lag time between ingestion of the drug and admission was 4.7 hours (range 1–26.2 hours).

The coingested drugs and their concentrations are summarized in Table 2.

In only 1 case, quetiapine was ingested as the sole drug. In all other cases benzodiazepines, antidepressants, or antipsychotics were coingested. In 6 patients, at least 1 of the coingested drugs appeared to be at a toxic serum concentration.

Liver and renal function tests stayed within the normal range (AST $\leq$ 40 U/L, ALT $\leq$ 45 U/L, and serum creatinine $<$ 150 µmol/L) in all cases.

The PSS was minor in 6 patients (43%), moderate in 5 patients (36%), and severe in 3 patients (21%). The types and frequencies of individual symptoms or signs used for estimating the PSS are summarized in Table 3.

In 3 cases the QTc interval was prolonged, without evidence of intrinsic cardiac toxicity. No correlation among the ingested doses, age, and PSS, was found (Fig. 1).

Gastric lavage and/or activated charcoal and a laxative were used for gastrointestinal decontamination in 12 cases. Except for gastrointestinal decontamination, no specific therapeutic measures were necessary in 8 cases. Two patients were treated with intravenous colloids because of hemodynamic instability. Four patients received intravenous flumazenil, in 3 cases because of coingested benzodiazepines and in 1 case as a diagnostic tool for suspected benzodiazepine intake. In 6 cases (43%) ICU admission was needed because of GCS $<$ 7, hemodynamic instability, and the need for intubation. One patient had a respiratory arrest but continued breathing after intubation. One other patient presented with dilated pupils and a GCS of 3 after ingestion of 2000 mg of quetiapine. Mechanical ventilation was not needed, and consciousness was restored within 24 hours. No patient developed seizures or died as a direct effect of quetiapine intoxication. Most patients recovered well within 2 days (range 1–4 days).

TABLE 1. Characteristics of Quetiapine-Intoxicated Patients

Characteristics	Cases
Median age at first intoxication* (y) (range)	32 (20–54)
Male/female* n (%)	3/6 (33/67)
Median ingested dose (mg)† (range)	2600 (1200–18,000)
Deaths (n)†	0
Median length of stay† (days) (range)	2 (1–4)
ICU admission† n (%)	6 (43)

*n = 9.
†n = 14 (including recidivists).

TABLE 2. Toxicity of Coingested Drugs

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Benzodiazepine	T	N	T	T	T	T	N	N	N			N	N	N
Antidepressant				T		T	N	N		N		N	T	N
Antipsychotic						T								
Other						T/N*								

T, toxic concentration; N, nontoxic concentration.
*Cisapride in toxic concentration, omeprazole in nontoxic concentration.
Concentrations were toxic if lorazepam $>$ 0.3 mg/L, diazepam $>$ 1.5 mg/L, nordazepam $>$ 1.5 mg/L, temazepam $>$ 1 mg/L, oxazepam $>$ 2.5 mg/L, fluoxetine $>$ 2 mg/L, citalopram $>$ 0.1 mg/L, zolpidem $>$ 0.5 mg/L, pipamperon $>$ 0.5 mg/L, cisapride $>$ 0.04 mg/L, and omeprazole $>$ 0.6 mg/L.[11]

Pharmacokinetics

No relationship was observed between the reported amount of quetiapine ingested and the serum concentration of quetiapine.

Table 4 shows the reported amount of quetiapine ingested, the lag time, and the serum concentration for each case. An elimination half-life could be calculated in 5 patients, and the median elimination half-life was 6.9 hours (range 4.3–14.6 hours). Elimination half-life was prolonged in cases 3 and 9. In case 3 a toxic amount, and in case 9 a nontoxic amount, of benzodiazepines was coingested.

TABLE 3. Severity of Effects Graded According to the PSS*

	PSS Grade		
Clinical Effect	Minor (n)	Moderate (n)	Severe (n)
Somnolence	8		
Coma (GCS 8–9)		3	
Coma (GCS $\leq$ 7)			3
Tachycardia			
100–140 ppm	9		
$>$ 140 ppm		1	
Hypotension			
Psys 80–100 mm Hg	4		
ECG QTc $>$ 450 ms	4		
Respiratory system: requiring extra oxygen		1	1 (arrest)
Rise of CPK 250 ~ 1500 U/L	1		
Rise of CPK 1500 ~ 10,000 U/L		1	

*PSS, Poisonings Severity Score.[9]

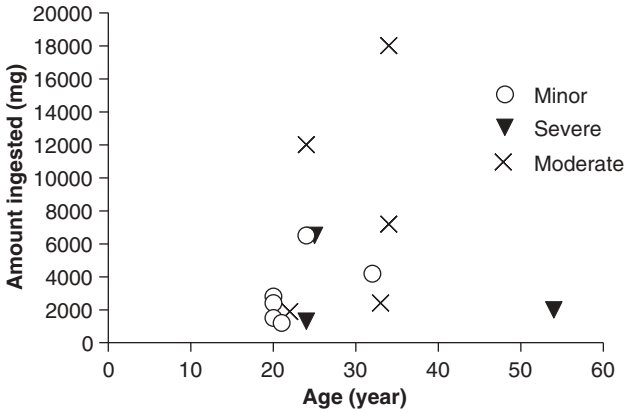

FIGURE 1. Relationships among age, reported ingested dose of quetiapine, and severity of intoxication as graded by PSS.

In 9 of the 14 cases, the suggested amount ingested did not correlate with the serum concentration measured. In all 9 cases serum concentrations were higher than expected, meaning that the amount ingested was probably higher than reported. This is exemplified in the concentration–time curve graph (Fig. 2) of case 3, who was reported to have ingested 7200 mg of quetiapine.

DISCUSSION

In our case series, no fatalities occurred from quetiapine overdose, although in 2 patients higher ingested doses were reported than have been associated with fatality in the literature.[6] Tachycardia and somnolence were the main clinical symptoms. The median duration of hospital stay was 2 days, similar to previous reports.[7] Admission to the ICU was not indicated in most cases. Only after the ingestion of a large dose of quetiapine and/or coingestion of other drugs in toxic quantities was observation in an ICU necessary.

A prolonged corrected QT interval was observed in 3 cases, but no intrinsic cardiotoxicity was established. Because no baseline electrocardiograms of these patients were available, no discrimination from possible underlying QT abnormalities could be made.[13] Similar to Balit et al,[7] no abnormalities in the uncorrected QT interval were seen in our case series, indicating that the prolonged QTc interval could be a direct result of the sinus tachycardia. No other clinically relevant cardiac abnormalities were observed in our case series.

However, because relatively limited data on quetiapine intoxications have been published at present, cardiac monitoring should be considered in cases of quetiapine overdose, especially if cardiotoxic drugs have been coingested. Whether quetiapine can exert a synergistic effect on the cardiotoxicity of other drugs is currently not known.

Based on our data, no relationship between the alleged amount of quetiapine ingested and the clinical outcome could be established, in contrast to the findings of Balit et al.[7] Several factors may contribute to this observation. First, taking a medical history from intoxicated patients (eg, the amount of drug ingested and the time of ingestion) is presumed to be unreliable. Second, the influence of gastric lavage and/or treatment with oral charcoal on the absorption of quetiapine is unknown but may have prevented absorption. Balit does not provide information on measures taken to prevent further absorption of the ingested drugs. In our hospitals, treatment with oral activated charcoal, together with a laxative, is common. Third, the time between ingestion and admission in the case series reported by Balit et al[7] was relatively short (median 1.2 hours, interquartile range 1–2.4 hours), whereas in our series the time to admission was much longer and had a wider range (median 4.7 hours, range 1–26.2 hours, interquartile range 2.7–8.1 hours). Fourth, coingested drugs may slow down or prevent the absorption of quetiapine (eg, anticholinergics), interact with quetiapine metabolism (eg, CYP P450

TABLE 4. Reported Amount Ingested Versus Serum Concentration of Quetiapine, Lag Time, and $t_{1/2}$

Case	Reported Amount Ingested (mg)	Serum Concentration (mg/L)	Lag Time (h)*	$t_{1/2}$ (h) (≥ 2 serum measurements)
1	18,000	1.1	12.8	—
2	12,000	8.8	1	4.3
3	7,200	2.5	26.2	14.6
4	6,500	3.5	10.3	6.9
5	6,500	5	7.3	—
6	4,200	3	2.8	—
7	2,800	4.1	3	6.7
8	2,400	3	6	—
9	2,400	5.5	2.2	10.3
10	2,000	4.5	6.3	—
11	1,900	1.8	4	—
12	1,500	2.5	3	—
13	1,300	3.5	5.3	—
14	1,200	3.1	2	—

*Interval between time of ingestion and blood sampling.

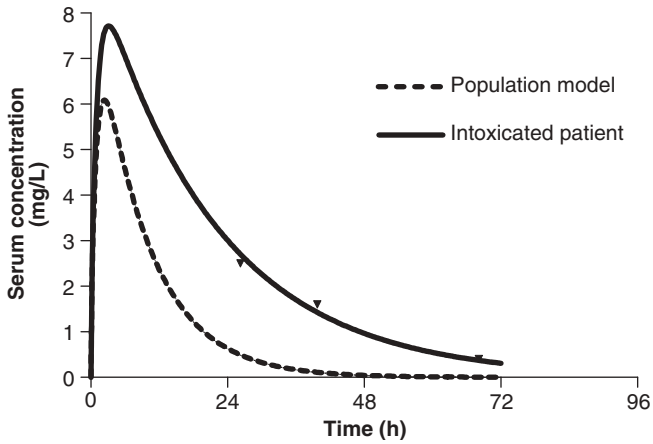

FIGURE 2. Serum concentration–time curve of quetiapine intoxication in case 3. Solid line, patient 3; dotted line, population curve.

3A4), or influence clinical symptoms by their own pharmacological effects.

To use a pharmacokinetic approach, with simulation of the serum concentration–time curve, time of ingestion and ingested amount must be known. Further, a reliable pharmacokinetic model for quetiapine must be available. However, it must be acknowledged that, in case of intoxication, one is never fully aware of the precise amount of drug ingested and the time of ingestion. Further, measures are taken to prevent further absorption of the ingested drug or drugs, and this raises a new confounder, the bioavailability of the ingested amount. These uncertainties all contribute to the error of the method we used. Knowing these sources of error, however, we put the obtained information into a pharmacokinetic model for quetiapine and fitted the model to the serum concentrations measured. We observed that in 9 out of 14 cases the serum concentrations measured were higher than our model predicted. This indicated that either the model was not correct or a higher dose had been ingested or ingestion had taken place later than reported. The model was obtained from schizophrenic patients who took normal doses and not from intoxicated patients. In cases of intoxication, saturation kinetics can occur with slowing of the elimination or drug–drug interactions that influence elimination. Because we did not observe a prolonged elimination half-life, saturation kinetics or drug–drug interactions are not a likely cause for the observation. Further, first-pass elimination may have been saturated; quetiapine has a bioavailability of at least 73%, and thus saturation may give an increase of bioavailability of 29% at maximum.[1] This may explain in part the difference between expected and measured serum concentrations. Therefore, we may conclude that with our pharmacokinetic model, assuming the time of ingestion was correct, it is possible to verify the reported ingested amount of drug and to estimate the peak serum concentration.

To determine an elimination half-life of a drug, two or more serum samples are needed. In clinical practice, however, it is hardly possible to obtain more than 1 blood sample because of limited logistics. Notwithstanding these limitations, we were able to estimate the quetiapine half-life in 5 of 14 patients; it was found to be somewhat prolonged in cases 3 and 9 and normal in the other cases. Because saturation kinetics were not likely, differences in metabolic capacity may have been the cause.

Although our results must be interpreted cautiously, given the limited number of patients, the sources of error in our pharmacokinetic estimations and the retrospective setup, they confirm previous observations about the relative safety of quetiapine intoxication.

CONCLUSION

We have found that quetiapine intoxications appear to proceed mildly. No fatalities occurred, and the prominent symptoms, tachycardia and somnolence, were transient. With regard to the pharmacokinetics of the drug, the elimination half-life was not prolonged, but probably, first-pass metabolism may be saturated in cases of overdose. Finally, the severity of the clinical symptoms was not correlated with the amount of quetiapine thought to have been taken.

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