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Clinical and analytical features of severe suicidal quetiapine overdoses – a retrospective cohort study

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Context. Detailed data on severe overdoses with quetiapine are relatively sparsely reported in the literature. *Objective.* To describe a cohort of 20 acute quetiapine overdoses and provide additional data on the pharmacokinetics and clinical features of intoxication with this drug. *Material and methods.* A retrospective study was conducted on patients with quetiapine poisoning admitted to our institution. We included moderate to severe overdoses between 2005–2011 who required admission to ICU. *Results.* Predominantly female patients (n = 17) ingested a median dose of 9.8 g quetiapine. Poison Severity Score was moderate in 9 patients, severe in 10 patients and in one case fatal. Quetiapine was analytically confirmed in all cases. Clinical manifestations included drowsiness or coma (all patients), tachycardia (12 patients) and hypotension (10 patients). Seizures and arrhythmia occurred in 4 patients, each. Intubation and mechanical ventilation was required in 14 patients due to seizures, respiratory depression or loss of airway protection and 15 patients developed pneumonia. Hypokalaemia and hyperglycaemia were present at admission in 10 and 5 patients, respectively. Despite frequent prolongation of the QT_c in 13 patients, QT interval was normal in most cases and QRS-interval was prolonged in only one patient. Presumably anticholinergic delirium was recognised in 8 patients and 6 patients received physostigmine with good clinical response. In 13 cases quetiapine was analysed quantitatively in serum with a relevantly prolonged half-life (16 ± 12 h) and a median peak serum concentration of 3074 ng/mL. In 4 of these 13 patients we observed an increase of quetiapine serum concentration in the further course. *Conclusion.* In this study, quetiapine overdoses were associated with significant toxicity and a fairly high number of complications. A careful and often prolonged clinical observation in the more severe cases of overdose seems mandatory.

Introduction

Quetiapine is a newer class of dibenzothiazepine antipsychotics and is increasingly used for the treatment of depression, bipolar disorders, schizophrenia, and sleep disturbances.[1,2] It has equivalent efficacy but superior tolerability compared to some other atypical antipsychotics regarding the incidence of extrapyramidal symptoms or endocrine disruptions.[3] However, despite generally considered being relatively benign in overdoses with a favourable risk-benefit profile of quetiapine[4], up to date there a number of single case reports with fatalities.[5,6] Over a ten-year period in England and Wales, there were 14 reported deaths involving quetiapine with the highest deaths per million prescriptions among all other antipsychotics, including clozapine and olanzapine.[7] Thus, quetiapine is not devoid of overdose toxicity. The main clinical manifestations of overdose are mild hypotension, central nervous system depression with the need for intubation and mechanical ventilation in some cases, and sinus tachycardia.[1,5,8,9] Cardiac dysrhythmias do occur infrequently and few patients are reported to develop seizures in large overdoses.[2,10] Quetiapine is described as the number one antipsychotic used for suicidal intended overdoses in some areas,[7] and there is an increasing number of studies with more detailed clinical and analytical data on severe cases of overdose. These include abstracts, single case reports, case series, some larger retrospective poison centre series and two large prospective studies.[2,8,9,11–17] However, some of these reports and series lack of clinical details or do provide only single quetiapine serum concentrations rather than a kinetic course. Thus, we decided to retrospectively perform an analysis of all moderate to severe quetiapine overdoses that were treated in our toxicological intensive care unit (ICU) and provide additional data on the pharmacokinetics and clinical features of intoxication with this drug.

Material and methods

Study design, setting and data collection

This study was a retrospective chart review of all patients of the toxicological ICU of Klinikum rechts der Isar, a 1100-bed tertiary care university hospital, that were admitted with the main diagnosis ‘acute quetiapine overdose’ between

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January 2005 and May 2011. Patients were identified by two of the authors (FE and RP) through a computerized search of an electronic clinical database (SAP ECC 6.0; Oracle database, release 10.2.0.4.0) and the data was entered in a prepared database sheet (Microsoft Excel). The search codes included quetiapine and/or Seroquel® and patients were included if they were admitted with acute ingestion of quetiapine requiring admission to ICU (e.g. coma, need for cardiovascular support, mechanical ventilation, haemodynamic monitoring, or seizures). Patients who coingested at least one additional psychopharmacological agent were only included if these coingested drugs were considered to play an only circumstantial role and quetiapine most certainly dominated this overdose. Patients who coingested more than one single psychopharmacaological agent (multiple coningestions) were excluded as the clinical picture of quetiapine overdose in these cases was considered markedly biased. These agents included serotonine reuptake inhibitors, neuroleptics, tri- or tetracyclic antidepressants, MAO-inhibitors, lithium, and valproic acid. Coingestion of doxylamine and diphenhydramine was also excluded, as these drugs would have considerably attributed to the development of anticholinergic delirium. Cases with inaccessible or incomplete charts were excluded as were mild to moderate intoxications that did not require admission to ICU.

A total of 68 retrieved cases of acute quetiapine overdoses that were admitted between 2005 and 2011 to our institution were primarily screened; 27 patients were excluded as they did not require ICU admission and could be managed in the ED or general ward; the remaining 41 patients were moderately or severely overdosed but 21 of these patients were excluded due to multiple coingestions (n = 15), incomplete data (n = 4) or inaccessible charts (2), resulting in a population of 20 patients that were finally included. Given the retrospective nature of this study, it was exempt from the assessment by the institutional ethics committee.

The charts were reviewed to obtain data on demographics, laboratory data and blood gas analysis on admission, blood pressure and heart rate, both in the preclinical setting as well as on admission, blood glucose obtained from blood-gas-analysis, and the Glasgow-coma-scale (GCS) as evaluated by the emergency physician. The ECG of each patient was reviewed manually for some variables (heart rate, QRS, QT and corrected QT-interval [QT_c], as well as arrhythmia). QT_c intervals were calculated using the Bazett formula. [18] The QT_c interval was considered abnormal if longer than 440 ms in men and 450 ms in women[19] as was the QRS interval longer than 120 ms.[20] Additionally, manually measured QT-intervals and heart rate of each patient, both obtained from the ECG at admission, were screened for risk stratification using the QT interval nomogram as suggested previously.[15,21] Lengths of stay in ICU and in hospital were recorded as well as medical interventions (e.g. drug administration, activated charcoal, intubation and mechanical ventilation, cardiovascular support). Complications (delirium, pneumonia, seizures, arrhythmia and death) were collected and severity of intoxication was assessed according to the Poison Severity Score (PSS).[22]

Analytical, pharmacokinetic and statistical analysis

Blood samples (in some cases serially) and urine samples at admission were screened using the Remedi HS® (Bio-Rad Laboratories, Inc., CA, USA) or TOX.I.S.® (Shimadzu Corporation, Japan) automated HPLC analyser. For quantitative analysis of quetiapine (or other coingestions) in serum LC-MS/MS was performed in some patients. The lower and upper limit of detection for quetiapine in serum was 5 ng/mL, and 2500 ng/mL, respectively. Concentrations above were determined after adequate dilution. The typical day-to day total coefficient of variation was 3.9% and the intra-assay coefficient of variation was 1.8%. Ethanol in serum (along with routine clinical chemical parameters) was quantified by our institutional laboratory. All the analysis being done on blood and urine samples where routinely performed immediately at that time when the patient was actually treated in our department, i.e. the results were already present in the patients' charts at the beginning of this study.

Terminal elimination half-life ($t_{1/2}$) of quetiapine was calculated from the patient's data if at least 3 or more serum concentrations were available. When appropriate, a one-phase exponential decay function was fitted to the data using GraphPad™ Prism (GraphPad Software, Inc., CA, USA). Elimination half-life was considered prolonged if it exceeded the population half-life of 6 h.[23] Data were entered and analysed using the PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, USA). The mean and the standard deviation (± SD) were used to describe quantitative data meeting normal distribution. Variables that were not normally distributed were expressed as the median and the interquartile range [IQR].

Results

We identified 20 patients that fulfilled our inclusion criteria with a median age of 38 years [IQR 25–75% 27–46]. They were predominantly female (n = 17) and ingested an estimated median dose of 9.7 g [2.7–14] quetiapine. In 6/20 of the cases, the ingested quetiapine was a sustained released preparation while 14 patients ingested an immediate release preparation. The median alleged time between ingestion and admission was 3.7 h [2.1–5.7] although this information could only be roughly estimated. There were six quetiapine mono-intoxications, five patients coingested sedatives (n = 3, lorazepam; n = 2 zopiclon [dose not known]) and three patients ingested quetiapine together with ethanol. Six patients coingested quetiapine together with another drug and in three of them ethanol was also ingested (median ethanol serum concentration 1.9 g/L [0.3–2.9] (n = 6). Of these six patients who coingested psychopharmacological agents (other than sedatives), three patients coingested cyclic antidepressants (n = 2 mirtazapine [1.2 and 1.3 g]; n = 1 nortriptyline [0.5 g]), one patient coingested risperidone [0.4 g] and two patients coingested citalopram [2.8 g in one patient, other dose unknown].

Treatment of patients included endotracheal intubation in 14 cases, ten patients required vasopressors (together with fluids) in the further course and 8 patients received activated charcoal via nasogastric tube, mostly as a single dose. Anticholinergic delirium was diagnosed in 8/20 of the patients that was incomplete in half of them (4/8). In those patients, the tetrad of the anticholinergic syndrome (mydriasis, tachycardia, dry mucous membranes, and delirium) was not completely developed, e.g. lack of tachycardia or mydriasis. Diagnosis of anticholinergic syndrome was made pretty late (median 14 h [5-66] after the alleged time of quetiapine ingestion; n = 8) and was suspected frequently after analgosedation has already subsided. Anticholinergic delirium was treated with phyostigmine (Anticholium®) in 6/20 of the patients with a median cumulative dose of 18 mg [3–48]. Two patients with anticholinergic delirium were not treated with physostigmine as they experienced seizures, either preclinical or shortly after admission. Clinical response to physostigmine was excellent in 5 patients (e.g. reduction in heart rate and agitation, ability to clearly communicate with the patient) and incomplete in 1 patient, thus requiring additional sedation with midazolam, haloperidol and lorazepam.

The majority of patients (15/20) developed pneumonia in their further course, either due to a presumed (micro-) aspiration in the preclinical setting or because of ventilator associated pneumonia that required subsequent antibiotic treatment. Seizures occurred in 4/20 of the patients, in one patient after the administration of flumazenil and in another patient shortly after administration of 2 mg of physostigmine. Four patients experienced arrhythmia: supraventricular tachycardia in one patient, atrioventricular nodal re-entry tachycardia in another patient; multiple premature ventricular beats in one patient and ventricular tachycardia in one patient (coingestion: citalopram) who died in a treatment refractory cardiac arrest that occurred 50 h after admission and was irresponsive to extracorporeal cardiovascular support. At that time, quetiapine in serum peaked extraordinarily high (about 20000 ng/mL), whereas citalopram in serum was 775 ng/mL (see Fig. 1, bottom panel).

For every patient ECG-data was available. In 10/20 of the cases an incomplete right-bundle branch block was diagnosed, however, it was unclear if this block was pre-existent or attributed to the poisoning. The QRS interval was normal in 19/20 patients (median 98 ms [90–101]) and prolonged (> 120 ms) only in the fatality. Despite a prolonged median calculated QT_c-interval (457 ms [425–458 ms]), the median QT-interval itself was normal in all cases (360 ms [314–395]). Based on the recently evaluated QT-nomogram,[21,24] the QT interval was considered normal in 11 patients, potentially at borderline risk (i.e. on the line of the nomogram) in 8 patients and only one patient had an abnormal QT, but in all of these cases heart rate was over 106 bpm.

Routine clinical chemistry at admission was predominantly normal, however, there was a trend for hypokalaemia (3.5 mmol/L [3.2–3.7]) and hyperglycaemia (124 mg/dL [102–143]). Details of the patients' baseline characteristics as well as clinical and analytical data are presented in Table 1 and 2, respectively.

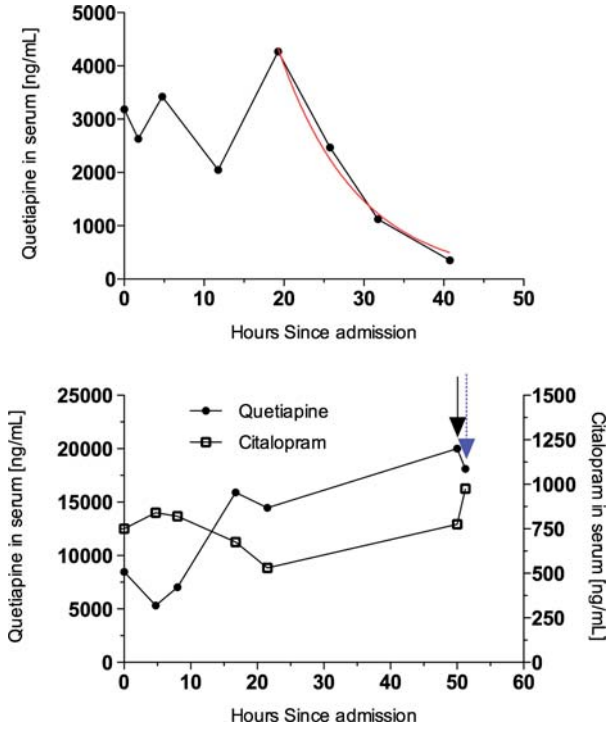

Fig. 1. Exemplary time course of quetiapine (top panel, 12 g ingested) and quetiapine/citalopram (bottom panel, unknown amount ingested) in serum over time. A one-phase exponential decay function (plateau set to zero) was fitted to the data for calculation of the terminal half-life (top panel, red curve). Both cases demonstrate undulating concentration profiles of respective drugs and illustrate the risk of delayed absorption in massive overdoses. Arrows in the bottom panel demonstrate extraordinarily high quetiapine serum concentrations before (solid arrow) ventricular fibrillation occurred and during (dotted arrow) advanced cardiac life support leading ultimately to death. Both patients did not receive activated charcoal (see colour version of this figure online).

Ingestion of quetiapine was confirmed qualitatively (HPLC) in all patients with quantitative data in 13/20 of the patients. In these patients, serial determination of serum concentrations allowed kinetic calculations. The median quetiapine concentration in serum at admission was 2529 ng/mL [2000–5226] and peaked at about 3074 ng/mL [2453–4344] with a median delay of 15 h [9–35] after admission. A re-increase of quetiapine in serum after concentration had initially declined was observed in 4/13 of the patients (exemplarily demonstrated in Fig. 1). Terminal half-life of quetiapine in serum was significantly prolonged (16 ± 12 h, n = 12), compared to a population based kinetic data of quetiapine being 6 h. Kinetic data as well as details of treatment and complications in each individual patient is summarized in Table 3.

Discussion

In this retrospective cohort, we demonstrated that severe quetiapine overdoses resulted in significant toxicity, in contrast to some other studies demonstrating a relatively good safety profile of quetiapine, even if overdosed.[4,8,15,25,26] Our data is in line with data of a 5-year retrospective case series where patients with quetiapine overdose, compared with all

Table 1. Baseline and clinical data of moderate to severe quetiapine overdoses (n = 20).

	Patients n = 20
Age (years)	38 [27–46]
Female	17 (85%)
Body weight (kg)	64 [58–96]
Estimated ingested dose (g)[a]	9.8 [2.7–14]
Slow release preparation	6 (30%)
Lag ingestion – admission (h)[b]	3.7 [2.1–5.7]
Treatment	
Endotracheal intubation[c]	14 (70%)
Preclinically	5 (25%)
At admission	9 (45%)
Mandatory ventilation	14 (70%)
Duration (h)	44 [31–69]
Activated charcoal	8 (40%)
Vasopressors	10 (50%)
Physostigmine treatment[d]	6 (30%)
Cumulative dose (mg)	18 [3.5–48]
Length of stay in ICU (days)	4 [1.6–4.7]
Length of stay in hospital (days)[e]	8 [5.2–10.8]
ECG-data[f]	
Incomplete right-bundle branch block	10 (50%)
QRS [msec]	98 [90–101]
QT_c [msec]	457 [425–485]
QT [msec]	360 [314–395]
Heart rate [bpm]	102 [82–115]
Complications	
Anticholinergic syndrome	8 (40%)
Incomplete	4 (50%)
Pneumonia	15 (75%)
Seizures	4 (20%)
Arrhythmia	4 (20%)
Death	1 (5%)

Data are expressed as median [IQR 25%–75%] for continuous variables and as frequency (n,%) for categorical variables.
[a]Ingested dose of quetiapine was estimated by anamnesis from relatives or empty blisters (n = 18). In n = 2 patients no such information could be obtained.
[b]Time between ingestion of quetiapine (estimated by anamnesis from relatives or the patient after intoxication subsided) and admission.
[c]Endotracheal intubation was instituted due to coma with loss of airway protection (n = 11) or cerebral seizures (n = 3).
[d]Physostigmine treatment was initiated in the case of severe central anticholinergic syndrome (mydriasis, tachycardia, dry skin, agitation) that was incomplete (e.g. absence of tachycardia) in 4 cases. Treatment was not initiated – for safety reasons – in two of the cases because of cerebral seizures.
[e]Length of stay in hospital does not necessarily reflect the time when medical treatment was still necessary but could be prolonged because of delayed transfer to a psychiatric ward.
[f]All ECG data was obtained from ECG at admission. Times were manually recorded and the QT_c was calculated according to Bazett´s formula.

Table 2. Clinical and analytical data of moderate to severe quetiapine overdoses (n = 20).

	Patients n = 20
Systolic blood pressure (mmHg)	
Preclinically[a]	110 [90–130]
At admission	110 [100–137]
Heart rate (bpm)	
Preclinically[a]	105 [90–130]
At admission	105 [80–123]
Glasgow coma scale[a]	8 [3–11]
Poison Severity Score[b]	
Mild	0
Moderate	9 (45%)
Severe	10 (50%)
Fatal	1 (5%)
Clinical chemistry at admission	
Na^+ (mmol/L)	139 [136–142]
K^+ (mmol/L)	3.5 [3.2–3.7]
Glucose (mg/dL)[c]	124 [102–143]
Creatinine (mg/dL)	0.7 [0.6–1.0]
Blood urea nitrogen (mg/dL)	11 [9–15]
Creatinekinase (U/L)	102 [60–510]
Leucocytes (G/L)	9 [6–12]
pH[d]	7.38 [7.34–7.45]
HCO_3^- (mmol/L)[d]	24 [21–25]
BE (mmol/L)[d]	−1.8 [–3.3–1.1]
Toxicological analysis	
Quetiapine qualitative (urine)[e]	20 (100%)
Quetiapine quantitative (serum)[f]	13 (65%)
Quetiapine conc. in serum at admission (ng/mL)	2529 [2000–5226]
Quetiapine peak-conc. in serum (ng/mL)	3074 [2453–4344]
Reincrease in quetiapine serum conc.[g]	4/13 (31%)
Time between admission and peak conc. (h)[g]	15 [9–35]

Data are expressed as median [IQR 25%–75%] for continuous variables and as frequency (n,%) for categorical variables.
[a]Systolic blood pressure, heart rate and the GCS-score were derived from the protocol of the ambulance or emergency physician.
[b]Severity of effects was graded retrospectively according to the Poison Severity Score (PSS).
[c]Glucose was determined preclinical in most cases or at admission before infusion of a glucose-containing solution.
[d]pH, HCO_3^- and BE were derived from blood arterial or venous blood gas analysis at admission.
[e]Quetiapine in urine was determined qualitatively using HPLC.
[f]Quetiapine in serum was determined quantitatively using LC-MS/MS.
[g]Quetiapine increased in serum after an initial decrease, probably because of delayed absorption (n = 4).

other antipsychotics as a group, were more likely to be comatose, had respiratory depression, and experienced hypotension requiring vasopressor support.[2] Compared to other second-generation antipsychotics, quetiapine accounted for the highest rate in major adverse effects, and death in a 10-year retrospective cohort study including 939 quetiapine overdoses.[27] In a large prospective study including n = 137 quetiapine alone overdoses, overdose results in severe toxicity in about one sixth of the cases. [15] In a retrospective series of 83 patients with quetiapine mono-intoxication reported to a poison control centre, severe symptoms (including coma, seizures, respiratory depression) occurred in 11 patients, all of those reported an ingestion of > 2.5 g.[9]

All patients in our series had a moderate or severe poison severity score and a fairly high rate of complications (e.g. seizures, arrhythmia) that occurred with one fatality. In the fatality, an unknown amount of citalopram was coingested together with quetiapine and we cannot exclude that this combination may have significantly increased cardiotoxicity. At the time when fatal arrhythmia occurred, citalopram serum concentration was 750 ng/mL. In 8 cases of fatal overdoses involving only citalopram, average post mortem blood concentration was 7000 ng/mL, whereas femoral citalopram blood concentration was 11600 ng/mL in another fatality.[28,29] Thus, fatal citalopram concentrations where about more than 10 times higher in these cases compared to our fatality. Citalopram alone seems therefore unlikely to explain the fatality, whereas the death is most likely due to the

Table 3. Detailed pharmacokinetic and clinical data of each patient with moderate to severe quetiapine overdose (n = 20).

Patient	Ingested dose [g][a]	Coingestion[b]	Quetiapine peak conc. in serum [ng/mL]	Delayed absorption[c]	Half-life [hrs][d]	Intubation/ Ventilation	Physostigmine	Activated charcoal [g]	Pneumonia	Seizures	Delirium	Arrhythmia[e]
1	30	LZP	6940	−	31	+	+	30	+	−	+	−
2	2	–	2529	−	20	−	+	−	−	+	+	−
3	20	–	2445	−	10	+	+	90	+	−	+	+ (VES)
4	NA	–	NA	NA	NA	+	−	20	+	−	−	−
5	12	–	NA	NA	NA	−	+	−	+	−	+	−
6	1	MIR; ETH (0.4)	NA	NA	NA	+	−	−	+	−	−	−
7	12	ETH (0.12)	4270	+	7 (terminal)	+	−	−	+	+	−	+ (AVNRT)
8	3	MIR	NA	NA	NA	+	−	50	+	−	−	−
9	8	CIT, ETH (1.98)	1554	−	6	+	−	−	+	−	−	−
10	12	–	6380	−	33	−	+	−	+	−	+	−
11	9	ZOP	3074	−	41	+	+	−	+	−	+	−
12	10	ZOP	2778	+	8	+	−	50	+	−	−	+ (SVT)
13	4.75	-	NA	NA	NA	+	−	10	+	−	−	−
14	1.25	ETH (1.87)	NA	NA	NA	−	−	−	−	−	−	−
15	20	NOR	4418	+	7	+	−	130	+	+	+	−
16	2	LZP	NA	NA	NA	+	−	−	−	−	−	−
17	9.7	LZP, ETH (2.8)	3137	+	5 (terminal)	−	−	−	−	−	−	−
18	12	RIS	2461	−	15	+	−	40	+	−	−	−
19	NA	CIT	20010	+	NA	+	−	−	+	+	+	+ (EMD, VT)
20	3	ETH (3.1)	1378	+	7 (terminal)	−	−	−	−	−	−	−
All	**12 [9-19]**		**3074 [2453-5399]**		**16 ± 12**							

Data are expressed as median [IQR 25%–75%] or mean ± SD for continuous variables. NA = not applicable. − = no; + = yes

[a]Ingested dose of quetiapine was estimated by anamnesis from relatives or the patient or by empty blisters.

[b]Coingestants: LZP = Lorazepam; MRT = Mirtazapine; CIT = Citalopram; ZOP = Zopiclone; NOR = Nortritptyline; RIS = Risperidone; ETH = Ethanol (g/L).

[c]Delayed absorption was anticipated if there was a clear reincrease in quetiapine serum conc. after an initial decrease. In two cases quetiapine increased within the first hours after ingestion but than steadily decreased reflecting more probably an incomplete absorption process rather than a delayed absorption.

[d]Half-life was calculated according to a 1-phase exponential decay function (plateau set to zero) that was fitted to the data using Graph-Pad Prism™ 5.0. In cases were a delayed absorption of quetiapine was observed, the terminal half-life was calculated after the maximal quetiapine peak. In the fatality (Patient 19) neither the ingested dose was known nor the concentration versus time profile of quetiapine allowed any reliable half-life calculation (see also Fig. 1).

[e]Arrhythmia: VES = ventricular extrasystoles; AVNRT = atrio-ventricular-nodal-reentry-tachycardia; SVT = supraventricular tachycardia; EMD/VT = electromechanical dissociation/ventricular tachycardia, leading to death finally.

combination of large quantities of citalopram and quetiapine. The fatality with co-ingestion of citalopram also experienced cerebral seizures. This is in line with data in the literature suggesting citalopram, when co-ingested with other psychoactive drugs – is associated with a greater risk of seizures and toxicity.[30]

Adverse effects associated with quetiapine use can mostly be explained by blockage of the alpha-adrenergic, muscarinic, histaminergic and serotonergic receptors resulting in orthostatic hypotension, tachycardia, sedation and hyperglycaemia.[2,8,11,31–35] Whereas most of these findings were also frequently observed in our cohort, some additional points deserve further discussion.

Pharmacokinetic aspects

To the best of our knowledge, a quetiapine peak serum concentration of about 20000 ng/mL is one of the highest ever reported, compared to peaks of 4220 ng/mL (36 g quetiapine, survived), 18300 ng/mL (11 g quetiapine, fatality), 12700 ng/mL (20 g quetiapine, survived), 12215 ng/mL (unknown amount, survived) or 20500 ng/mL (24 g quetiapine, survived), respectively.[3,12,17,33,34] The severity of quetiapine overdose seems not being associated with either high serum concentrations or the reported ingested dose in one study whereas probability of intubation was reported to be higher in patients ingesting larger doses of quetiapine in one large prospective study.[8,15] Based on our data, no relationship between the alleged amount of quetiapine ingested and the clinical outcome could be established.

Pharmacokinetic profiles of quetiapine in overdosed patients are not frequently reported in the literature. In a series of 14 quetiapine overdoses, serial measurement was performed in only 5 patients without discussion of the reported half-life.[8] The calculated median apparent half-life of quetiapine overdoses treated with activated charcoal is reported to be 6.6 h [4.9–8.4].[16] The mean (terminal) half-life of quetiapine in our series is substantially longer corresponding to a reported half-life of around 17 h in one case after ingestion of an unknown amount of quetiapine with a peak serum concentration of 12215 ng/mL.[17] The shorter half-life mostly reported in literature (approximately 4-8 hours) may be due to a combination of primary drug distribution into tissues and elimination from the body, as suggested previously.[33] Peak plasma concentrations of quetiapine normally occur within 1–2 hours after oral administration. In line with others, we observed remarkably delayed peak concentrations in our patients not only after ingestion of sustained release (6/20) but also immediate release preparations (14/20; see also Fig. 1). Redistribution of quetiapine, bezoar formation or delayed absorption from the gut because of anticholinergic effects of quetiapine as well as the sparse use of activated charcoal in our series leading to a second peak of quetiapine may be some explanations.[33] This may be associated with a rather late occurrence of sometimes life-threatening symptoms, as demonstrated with our fatality that experienced life-threatening dysrhythmias not earlier than 50 hours after admission.

Cardiovascular effects

Cardiotoxicity of quetiapine as demonstrated by changes in the ECG was, at best, only moderate and QRS-interval prolongation was only seen in our most severe (and fatal) case. This series along with other studies demonstrates that QT_c prolongation is commonly associated with quetiapine overdose although the significance of this association remains unclear.[25,33] It has been repeatedly shown that Bazetts formula significantly overcorrects for fast heart rates and significantly undercorrects for slow pulse rates.[11,15,36,37] Thus, the QT_c-prolongation seen in 15/20 of our patients is most likely a result of sinus tachycardia causing overcorrection of the QT interval by Bazetts formula, rather than intrinsic cardiac toxicity of quetiapine, as QT remains unchanged.[11,33] This is supported by the relatively normal uncorrected QT-time in 19/20 of our patients. For a more appropriate risk assessment of the QT interval it is therefore suggested to use a QT-nomogram as recently evaluated.[21,24] In line with a study of n = 137 quetiapine alone overdoses where 9% of the patients had abnormal QT-intervals,[15] only one patient of our cohort had an abnormal QT-interval based on the evaluated QT nomogram, but heart rate in this case was 117 bpm. It is known that the majority of cases of torsades de pointes in patients with prolonged QT interval do only occur with heart rates less than 100 bpm.[38]

Nonetheless, one has to consider that arrhythmia occurred in 4 patients and only the fatality coingested citalopram. In the remaining three patients with cardiac arrhythmia, there was one quetiapine mono-intoxication, one zopiclon-coingestion and one patient who additionally ingested ethanol (0.12 g/L in serum), conditions where additional cardiotoxicity of the coingested drug is unlikely.

Quetiapine-induced delirium

Few sources report delirium as a likely consequence of overdose with quetiapine alone.[15,39] Of note, we observed a high incidence of anticholinergic delirium that may be misdiagnosed, as the classical tetrad may be absent (in 4/8 of our patients). Quetiapine has been reported to have moderate antagonistic action at M_1-muscarinic receptors that may result both, in anticholinergic-mediated tachycardia, and delirium.[11,15,31,40] This is supported by the fact that most of our patients with suspected anticholinergic delirium (8/20, 6 of them received physostigmine) responded promptly (reduction in heart rate and reversal of agitation) to a single intravenous dose of 2 mg physostigmine. Due to its relatively short half-life (15–40 min) compared with that of quetiapine, it had to be infused continuously (up to 2 mg/hour) in 3/6 of our patients for sustained clinical effect. Two patients with suspected anticholinergic delirium did not receive physostigmine due to previous seizures, requiring sedatives (benzodiazepines or propofol) instead and the clinical responsiveness was, at best, moderate. Even though the use of physostigmine is not without risk, its causative mechanism of action in anticholinergic delirium seems favourable over benzodiazepines that may also lead to significant side effects (e.g. pronounced sedation, respiratory

depression, aspiration). Physostigmine has been used successfully for patients with anticholinergic delirium associated with typical and atypical neuroleptics and it is considered safe provided that the ECG does not demonstrate cardiac conduction disturbances (e.g. prolonged PR or QRS intervals).[41] None of our patients who received physostigmine did have prolonged PR or QRS intervals and these cardiac conduction disturbances are not typically related with quetiapine overdoses, although a number of quetiapine overdose reports describe QRS interval prolongation similar to the Type 1_A antiarrhythmics.[4]

Limitations

Despite the possible valuable implications of this study, however, we have to account for some important limitations. First, it was a retrospective study suffering from the intrinsic limitations of a retrospective chart review, including incomplete recording of data in the charts. Second, we only included patients with quetiapine overdose requiring ICU-admission rather than including all quetiapine overdoses that were admitted to our institution. Thus, the conclusions drawn from this study cannot be generalized to a larger population of quetiapine overdoses, which is an important selection bias. Third, we included also non-solely quetiapine overdoses even if the majority (14/20) of patients did not coingested drugs with known additional risk of e.g. cardiotoxicity. However, we have to be aware that a more pronounced coma due to coingested sedatives or alcohol (with the need for intubation and mandatory ventilation) might have biased the picture of severity. It is further unclear if the coingestants may have influenced both, the clinical and pharmacokinetic course of quetiapine overdose. Fourth, the information regarding the alleged ingested dose and time may not be precise in all cases, thus correlations between dose and clinical effect may be hampered.[8]

In conclusion, quetiapine overdose requiring admission to ICU in this series was associated with a high need for mandatory ventilation (and development of subsequent pneumonia), the frequent need for vasopressors and a relatively high rate of complications regarding anticholinergic delirium, seizures and arrhythmia. Careful attention to prevent patient deterioration, especially in the later phase after quetiapine ingestions, should be applied to these patients to reduce complications after quetiapine overdoses.

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Declaration of interest

The authors report no declarations of interest.

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The Poison Review

Massive quetiapine overdose causes delayed cardiotoxicity

December 11, 2011, 3:35 pm

Clinical and analytical features of severe suicidal quetiapine overdoses – a retrospective cohort study. Eyer F et al. *Clin Toxicol* 2011;49:846-853.

Abstract

Quetiapine (Seroquel) is an atypical antipsychotic agent that blocks muscarinic, α-adrenergic, histaminic, and serotonergic receptors. Major toxic manifestations include hypotension, CNS depression, tachycardia, seizures, and delirium (presumably anticholinergic. Although some literature has stated that quetiapine is relatively safe, overdose deaths have been reported. In fact, this paper point out that in Great Britain, quetiapine has been associated with the highest incidence of fatality among all the antipsychotics.

This retrospective review of 20 cases of confirmed severe quetiapine overdose requiring ICU admission obviously involves a highly selected group of patients, making it hard to generalize the findings. However, there are some valuable take-home points:

1. The median dose of quetiapine in these cases was 9.7 gm (range, 2.7 – 14).
2. Half-life was prolonged and peak level of quetiapine were delayed in these massive ingestions, both in patients who took sustained-release preparations (6/20) and those who too the immediate-release form (14/20).
3. Seizures occurred in 4 patients, in one case after administration of flumazenil, and in another after 2 mg physostigmine.
4. Of 8 patients who developed delirium, 6 were treated with physostigmine. Clinical response was described as "excellent" in 5 and "incomplete in one. (it is not clear to me where the patient who developed seizures after physostigmine fits in here.)
5. Half the patients who had delirium (presumably anticholinergic) did not have all classic signs of anticholinergic toxicity.
6. Only four patients had cardiac dysrhythmias. One of these patients developed ventricular tachycardia and irreversible cardiac arrest. (This patient had extremely high quetiapine levels and had also ingested citalopram [Celexa]).
7. In the fatal case, onset of life-threatening arrhythmia was at 50 hours.
8. Physostigmine is contraindicated in patients who have cardiac conduction disturbances such as prolonged PR or QRS intervals.

Probably the most important thing to be learned from this paper is that in massive overdose of quetiapine, fatal consequences can be delayed up to 50 hours after ingestion, if not beyond. Therefore, these patients require prolonged observation in a monitored or intensive care setting.

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