**Is Quetiapine Safe in Overdose?: A Case Report and Literature Review**

**Ketyapin Doz Aşımında Güvenli mi?: Olgu Sunumu ve Literatürün Güzden Geçirilmesi**

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**ABSTRACT**

Quetiapine is an atypical antipsychotic medication used in the management of affective disorders and schizophrenia, in which suicide attempts are not infrequent. A favorable risk/benefit profile of quetiapine has been reported in the literature, but data on its overdose are only sparsely available. In this article, we present the case of a 25-year-old female patient with bipolar disorder to highlight the safety of quetiapine overdose. She had seven previous impulsive suicide attempts in mixed episodes. She was found unconscious after ingesting 9 grams of quetiapine. Recovery was obtained with supportive treatment. Quetiapine has greater safety in overdose than the traditional antipsychotic agents. With good supportive care, of overdose symptoms typically resolve within 24 hours and none of the side effects are irreversible. Quetiapine is an antipsychotic of choice in patients with risk of medication-based suicidal attempts. (Archives of Neuropsychiatry 2012;49: 157-159)

**Key words:** Quetiapine, overdose, pharmacokinetics, coma, suicide

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**Introduction**

Quetiapine fumarate is an atypical antipsychotic medication FDA approved and used for the treatment of affective disorders and schizophrenia, and is used off-label in the management of several other psychiatric disorders. Since affective disorders and schizophrenia are chronic and debilitating life-long illnesses, suicide attempts are not infrequent (1,2).

A favorable risk/benefit profile of quetiapine is reported in the literature, but data on its overdose are only sparsely available (1). The main clinical findings in quetiapine overdose resulting from α-adrenergic and histamine receptor blockade are hypotension, tachycardia and somnolence. Potentially life-threatening consequences from overdose include QT prolongation and respiratory depression. Overdoses with up to 20,000 mg have very seldom been noted to result in fatalities (1,2,3).

We present a case to highlight the safety of quetiapine overdose.

**Case**

We present the case of a 25-year old female patient with a 13-year history of bipolar disorder. She had eight previous psychiatric hospitalizations, seasonal characteristics of her illness, seven previous suicide attempts and rapid cycling episodes in the last year. She was found unconscious by her husband. Although information concerning the amount and the time of drug ingestions were not totally reliable, it was learned that she had an impulsive suicide attempt by ingesting 30 tablets of 300 mg quetiapine. There was no history of other coingestants. When she was taken to hospital, she was comatose and in...
respiratory distress. Admission to the intensive care unit was indicated and mechanical ventilation was required. Her score of Glasgow Coma Scale was 3. Aspiration, forced diuresis, gastric lavage and oral active charcoal were administered. She had sinus tachycardia (138 ppm) and hypotension (70/30 mmHg). She regained alertness and had spontaneous respiration approximately four hours after presentation and was extubated. She recovered uneventfully and was transferred to a psychiatric facility 24 hours later. Her hypotension (range 80/60 to 90/70 mmHg) and tachycardia (120 ppm) persisted for another 24 hours. Forty-eight hours later, lithium (900 mg/day), valproic acid (500 mg/day) and olanzapine (20 mg/day) were initiated since mixed mood symptoms emerged.

Discussion

Quetiapine is well absorbed, and reaches peak serum concentrations at 1.5 hours after oral administration. It is extensively protein-bound, and has a high volume of distribution. Quetiapine is metabolized by hepatic cytochrome P450 isoenzyme 3A4, and is mainly excreted in the urine as inactive metabolites (4). Quetiapine has a safety record in overdose (1). Quetiapine toxicity is defined as a serum concentration >0.5 mg/L. The observed physiological effects of overdose represent exaggerated manifestations of the predicted receptor effects of the drug (2). Quetiapine overdose can cause multiple types of cardiovascular effects including tachycardia, hypotension and an increase in the QRS and QTc intervals. Anticholinergic effects like constipation, dry mouth and decreased bowel movements are also possible. Quetiapine overdose also may cause central nervous system (CNS) depression and delirium (3,4). also may cause central nervous system (CNS) depression and delirium (3,4). Seldom, in massive overdoses it can lead to extrapyramidal effects and seizures. Hypokalemia and rhabdomyolysis may also be seen in laboratory findings (3).

Alone or in combination with other medications, quetiapine overdose has resulted in QT prolongation (5), loss of consciousness (6), sinus tachycardia (7) and hypokalemia with first-degree heart block (8). Most of the reported patients recovered with symptomatic and supportive treatment. Medical comorbidity in extreme overdoses may contribute to a fatal outcome. In such a case, a male schizophrenic patient with cardiac dysrhythmia and hypertension who had a history of QT prolongation with risperidone overdose, died after a quetiapine overdose with an estimated 10,800 mg (with serum level 18,300 ng/ml) (1). Three additional cases were found dead (9). According to the product monograph, six acute overdoses ranging from 1,200 to 9,600 mg occurred during premarketing clinical trials and none resulted in death (2).

In two case-series studies, tachycardia and somnolence were cited as the main clinical symptoms (10,11). The most consistent cardiac finding in overdose is sinus tachycardia, which results from the anticholinergic properties of the drug (2,5,6,10,11). As might be expected by its α1 blocking features, hypotension can occur but is reported to be rare (2,11). Somnolence and hypotension resolve within approximately a day, whereas tachycardia persists into the second day in almost all cases (2,7,12). Hypotension and tachycardia both persisted two days in our case. Prolonged QTc is likely to be a result of an overcorrection caused by the tachycardia. Self-limiting QTc interval prolongation was reported in two cases (5,12). A case report documented prolonged QT interval following 10,000 mg ingestion of quetiapine and comedication with fluvoxamine, which might have increased the propensity of toxicity. The patient was comatose, hypotensive, tachycardic and was intubated. His tachycardia resolved by the third day (5). There was no QTc prolongation in our case. QRS widening may be corrected with sodium bicarbonate (4). QTc prolongation requires correction of potential contributing causes such as hypokalemia and hypomagnesemia. Torsades de pointes should be treated with IV magnesium sulfate. Sinus tachycardia should not be treated unless associated with active ischemia that is rare, but may complicate overdoses in patients with existing coronary disease. Hypotension can be treated with fluids and vasoconstrictors such as norepinephrine or phenylephrine, but because quetiapine is a potent α1 receptor antagonist, vasopressors with β2 activity such as epinephrine or isoproterenol may worsen the hypotension (13).

In large overdoses, patients may require intubation and ventilation for associated respiratory depression, which was the case in our patient. Another case report also documented acute respiratory distress syndrome (14). No acute organ toxicities or malignant cardiac arrhythmias have been reported (15). In a case with 12 g overdose, confusion, sinus tachycardia and rapidly evolving rhabdomyolysis were described (16). Seizures are possible, but generally are short-lived and often require no pharmacological treatment (13). In a case with a massive overdose of 24 g, coma, myoclonic jerks and generalized seizures were reported and benzodiazepines were administered (13).

In the series of 14 cases, dose range was 1,200-18,000 mg. Severity of intoxication was not found to be associated with a higher amount of intake and no correlation was found between the serum concentration of quetiapine and the amount ingested. Apart from the clinical symptoms, knowledge in the pharmacokinetics of drugs in overdose can play an important role in the treatment. Medications with large volume of distribution like quetiapine may have their half-life underestimated during studies done with normal doses in healthy volunteers. This may account for the poor prediction of duration of effects and persistence of serum concentrations (2). The absorption of quetiapine occurs during the first two hours after ingestion. In overdoses, it appears that much of the quetiapine is not absorbed. Potential local anticholinergic effects might reduce absorption (2). It has been demonstrated that pharmacokinetics of quetiapine differs substantially in the overdose patients. The plasma elimination occurs in a multiphasic fashion (17). Because of rapid redistribution to tissues, final elimination occurs approximately 36 hours later at a much slower rate, most probably reflecting the redistribution from tissues into blood. This explains why clinical manifestations can be observed up to two days, as was the case in our patient.

There is no specific antidote and quetiapine overdose is managed by appropriate supportive measures including: gastric lavage and administration of activated charcoal and a laxative, maintaining airway and ensuring adequate ventilation and oxygenation, and cardiovascular monitoring (18). The influence of gastric lavage and treatment with oral charcoal on the absorption...
of quetiapine is unknown, but may prevent absorption (10). Isbister et al. showed that activated charcoal decreased absorption even when given more than one hour after ingestion of quetiapine. Charcoal was estimated to reduce fraction absorbed by 35% (19). The latency from ingestion to presentation might have been more than 1.5 hours in our case too. Because relatively limited data on quetiapine intoxications have been published, cardiac monitoring should be considered especially if cardiotoxic drugs have been coingested.

Minor symptoms are hypotension (80-100 mmHg), somnolence, tachycardia (100-140 ppm), minor ECG changes and mild rise of CPK (250-1,500 U/L). Moderate symptoms are coma, tachycardia (>140 ppm), hypotension (<80 mmHg), major rise of CPK (1,500-10,000 U/L) and alterations in respiratory status. Severe symptoms are coma and respiratory arrest. Although the lack of monitoring serum quetiapine level is a limitation in our case, the clinical symptoms and vital signs that required mechanical ventilation were in line with high-dose intoxication. Nevertheless, 24 hours later, the only symptoms were tachycardia and hypotension, and the patient was discharged form ICU and referred to our psychiatry unit. The intoxication also did not adversely affect the reinstition of three psychotropic medications 48 hours later.

The consensus statement accepts the use of high-dose antipsychotic medication for certain patients in certain situations (20,21). Quetiapine fumarate appears to have greater safety in overdose than the traditional antipsychotic agents and its toxicity is consistent with its receptor profile. With good supportive care, the overdose symptoms typically resolve within 24 hours. Risk of death in quetiapine overdose appears to be low when supportive measures prevent vasodilatory shock. None of the effects are irreversible. This report supports the literature suggesting quetiapine as a relatively safer-in-overdose antipsychotic and an antipsychotic of choice in patients with risk of medication-based suicidal attempts.

References