Use of intravenous lipid emulsion in the resuscitation of a patient with cardiovascular collapse after a severe overdose of quetiapine

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Background. Quetiapine is an atypical antipsychotic medication that is increasingly being used in the treatment of psychotic disorders and depression. An overdose of quetiapine is associated with hypotension, sinus tachycardia, and sedation. The clinical effects of its overdose are often mild to moderate, but a severe overdose can cause cardiovascular collapse and death. Intravenous lipid emulsion (ILE) is a proposed treatment for potentially lethal cardiotoxicity after severe overdoses with lipophilic drugs, such as quetiapine, mainly by the sequestration of the lipophilic toxin to an expanded intravascular lipid phase. Objectives. To report a case where ILE was successfully used in the resuscitation of a patient with cardiovascular collapse after a severe quetiapine overdose. Case report. A 42-year-old woman was admitted to the Emergency Department after being found unconscious at home, due to an estimated ingestion of 24 g of quetiapine (Seroquel). She was initially cardiopulmonary stable and unresponsive with a Glasgow Coma Scale of 3. The patient was immediately admitted to the Intensive Care Unit, where her condition quickly deteriorated. She was intubated, due to loss of airway. In addition, a gastric lavage was performed and activated charcoal was administered. The patient presented with cardiovascular collapse refractory to vasopressor treatment and volume resuscitation. ILE bolus followed by continuous infusion was administered. Her blood pressure started increasing 5 min after ILE was initiated and within an hour circulation was stabilized. The patient recovered completely without any residual symptoms, after 3 days in the ICU. Conclusions. ILE may potentially be life-saving in cases of severe quetiapine poisoning and should be considered as a treatment for severe cardiovascular instability resulting from quetiapine poisoning refractory to maximum conventional therapy.

Keywords Cardiac support; CNS/Psychological; Heart

Introduction

Quetiapine is an atypical antipsychotic medication that is increasingly being used for the treatment of depression, bipolar disorders, schizophrenia, and sleep disturbances. The number of poisonings caused by an intentional drug overdose with quetiapine is increasing. The clinical effects of a quetiapine overdose are often mild to moderate in severity and include hypotension, sinus tachycardia, respiratory depression, and coma. Cardiac dysrhythmias, prolongation of the QTc- and QRS-interval do occur frequently. Ingestion of more than 5 g quetiapine can result in symptoms of severe overdose, but the correlation between dosage, serum drug concentration, and severity of the symptoms is poor. Death following a quetiapine overdose is a rare consequence. However, compared with other atypical antipsychotic medication, patients with quetiapine overdose suffer the highest rate of serious adverse effects and death.

Intravenous lipid emulsion (ILE) is a recommended treatment for local anesthetic-induced cardiovascular collapse. In cases of overdose of non-local anesthetic lipophilic drugs, data from animal experiments and human cases suggest that ILE may be effective in the amelioration of potentially lethal cardiotoxicity.

The proposed predominant mechanism of action is the sequestration of the lipophilic toxin into an expanded intravascular lipid phase. Toxicity is hence reduced by lowering concentration of the toxin at the effect site. The ability of lipid emulsion to bind a drug is largely dependent on the drug’s partition constant and volume of distribution, since they reflect the degree of lipid solubility of the drug. Thus, partition constant and volume of distribution are predictors of clinical efficacy of ILE. Quetiapine is a lipophilic drug with a partition constant (log P) of approximately 2.1 and a volume of distribution of 10 L/kg. Compared with other cardiotoxic lipophilic drugs, quetiapine has a lower degree of lipid solubility than most tricyclic antidepressants and typical antipsychotics. However, the lipid binding properties of quetiapine is similar to
the properties of the local anesthetic bupivacaine, for which numerous case reports have shown that ILE is effective. Patients with severe quetiapine overdose could benefit from ILE; however, evidence in the literature is sparse. A description of a case of cardiovascular collapse after a severe quetiapine overdose, where ILE was potentially life-saving, follows.

**Case report**

A 42-year-old woman was brought to the Emergency Department (ED) after being found unconscious at home due to an estimated ingestion of 24 g of quetiapine (Seroquel). The time of ingestion was unknown. She had a history of schizoaffective disorder with several previous intentional drug overdoses. In the ED the woman presented with a Glasgow Coma Scale of 3, her blood pressure was 90/60 mmHg, pulse rate was 95 bpm, ECG showed sinus rhythm without prolongation of the QTc- and QRS-interval, and the room air SpO2 was 97%. She was immediately admitted to the Intensive Care Unit (ICU), where shortly afterwards, her condition quickly deteriorated. The patient was intubated and subsequently ventilated due to loss of airway. A gastric lavage was performed and small amounts of tablet fragments were observed. A dose of 50 g of activated charcoal was administered via a nasogastric tube. The blood gas analysis showed a metabolic acidosis with pH 7.26 and BE -6.2. A dosage of 120 mmol of sodium bicarbonate (NaHCO3, 50 mg/mL, Fresenius Kabi) and 20 mmol of magnesium sulphate was administered intravenously. The ECG showed sinus tachycardia with 133 beats/min, and a widened QRS interval (104 ms) and prolongation of the QTc interval (467 ms). The patient was hypothermic with a core temperature of 34.7°C. Her systolic blood pressure remained below 50 mmHg, despite vasopressor treatment with an infusion of norepinephrine 0.8 μg/kg/min, and repeated injections of epinephrine (0.3 mg in total) and phenylephrine (0.8 mg in total). Volume resuscitation was given with 2 L of Ringer's acetate, 100 mL albumin 200 g/L (Albunorm®, Octapharma) and 500 mL hydroxyethyl starch 60 mg/mL (Venofundin®, Braun). However, the cardiovascular collapse was refractory to vasopressor treatment and volume resuscitation, and her blood pressure continued declining. An immediate circulatory arrest was impending and transfer to a unit, within our hospital, that has facilities for extracorporeal circulatory support (ECCS) was considered. Subsequently, a single 170 mL bolus of 20% lipid emulsion (Intralipid®, Fresenius Kabi) was given intravenously, followed by an infusion of 500 mL 20% lipid emulsion run over 1 h (Figure 1). Approximately 5 min after the single bolus of lipid emulsion was given, the systolic blood pressure had increased from 50 to 75 mmHg. Within the first hour after initiating ILE, her circulation was stable with continuous infusion of norepinephrine at 0.8 μg/kg/min, and no further boluses of either epinephrine or phenylephrine were needed. The systolic blood pressure was 110 mmHg and the mean arterial pressure was 65 mmHg. Three hours after ILE, hemodynamic monitoring using PiCCO (Pulsion Medical Inc.) revealed a hyperdynamic circulation with PCCI of 7.0 l/min/m² and a marked vasoplegia with a SVRI of 610 dynes·sec·cm⁻²·m⁻², despite continuous infusion of norepinephrine at 0.8 μg/kg/min, and no further boluses of either epinephrine or phenylephrine were needed. The systolic blood pressure was 110 mmHg and the mean arterial pressure was 65 mmHg. Three hours after ILE, the QTc interval was normalized and the high dose vasopressor support with norepinephrine could be significantly reduced and subsequently

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**Fig. 1.** Systolic blood pressure relative to interventions during the critical phase.
discontinued. The circulation remained stable. The patient was weaned and extubated 18 h after ILE. Blood samples taken when the patient was stabilized showed serum creatinine 150 μmol/L, troponin T 360 ng/L, and myoglobin 396 μg/L. All the values were normalized within 3 days and the patient presented no clinical symptoms of malignant neuroleptic syndrome. The echocardiography performed on the third day was normal, with an ejection fraction of 60%. The patient was transferred to a medical ward on the third day and on the fourth day she was able to be discharged to a psychiatric ward, as, by then, she was physically fully recovered.

The serum quetiapine level at the time of the cardiovascular collapse was 38,350 ng/mL, which is an exceptionally high concentration. Twenty hours after ILE it had dropped to 3068 ng/mL. The lipid was not separated from the serum prior to the second measurement.

Discussion

Quetiapine is a dibenzothiazepine derivative with multiple receptor antagonist properties. It has a weak affinity for dopamine (D₁, D₂), and serotonin (5-HT₁A) receptors and a moderate to high affinity for muscarinic (M₁), histamine (H₁), serotonin (5-HT₂A), and adrenergic (α₁) receptors. Its α₁-adrenergic receptor antagonism may produce hypotension with reflex tachycardia, symptoms which were well pronounced in our patient. The H₁-histamine receptor antagonism of quetiapine may confer central nervous depression and hypotension. Its antagonistic actions at M₁-muscarinic receptors can produce central and peripheral anticholinergic toxicity. Its antagonistic actions at M₁-muscarinic receptors can produce a prolongation of the QRS interval and risk for ventricular dysrhythmia. The sodium channel blocker toxicity can be reversed with the administration of physostigmine, a cholinesterase inhibitor.²

Cardiac dysrhythmia after poisoning with psychiatric medication can be caused by sodium channel antagonism, producing a prolongation of the QRS interval and risk for ventricular dysrhythmia. The sodium channel blocker toxicity, often described as ‘membrane stabilizing effect’, is a known property of tricyclic antidepressant (TCA) overdose toxicity. Quetiapine is a tricyclic compound and thus resembles TCA structurally. Quetiapine can also cross react in TCA immunoassays.¹¹ The affinity of quetiapine for cardiac sodium channels is not well described, but a number of case reports and review articles on quetiapine overdose report that QRS interval prolongation does occur infrequently.¹²

Cardiac dysrhythmia after poisoning with psychiatric medication can also be due to potassium channel antagonism, producing QTc interval prolongation with risk for developing torsade de pointes. Similar to typical antipsychotics, quetiapine overdose can produce QTc interval prolongation, although the clinical significance of this remains unclear.²,¹² It is worth considering that quetiapine toxicity often presents with tachycardia, and Bazett formula for correction of the QT interval has been shown to overcorrect fast heart rates.¹³,¹⁴ The majority of cases with torsade de pointes in patients with prolonged QT interval occur with heart rates less than 100 bpm. Our patient was tachycardic and had a significantly prolonged QTc interval; however, the uncorrected QT interval was not prolonged and no ventricular dysrhythmia was seen. Thus, the QTc interval prolongation might have been a result of sinus tachycardia causing overcorrection of the QT interval by Bazett’s formula.

Quetiapine is rapidly absorbed after oral administration, reaching peak plasma concentration (tmax) after 1–2 h.⁹ In overdosed patients, the tmax can be remarkably delayed, presumably due to bezoar formation or delayed absorption from the gut because of the anticholinergic effects of quetiapine.² It is highly protein bound (83%), highly lipophilic, and accumulates in the brain and other tissues. The volume of distribution (Vd) is large, 10 L/kg.⁰ These pharmacokinetic properties make its removal by hemodialysis ineffective. The liver extensively metabolizes quetiapine via CYP3A4 sulfoxidation and oxidation. Metabolites are pharmacologically inactive.¹⁰ The mean elimination half time (t½ (mean)) in therapeutic dosage is 4–10 h. In overdosed patients treated with activated charcoal, the calculated median, apparent half-life of quetiapine is reported to be 6.6 h (4.9–8.4).¹⁵ Some studies report significantly longer t½ in overdosed patients.

The severity of symptoms in cases of quetiapine overdose correlates poorly with serum concentration and the ingested dose.¹⁶,¹⁷ At the time of the cardiovascular collapse, our patient had a serum concentration of 38,350 ng/mL, which, to the best of our knowledge, is the highest ever reported, compared to peaks of 18,300 ng/mL (11 g quetiapine, fatality) or 20,500 ng/mL (24 g quetiapine, survived), respectively.² However, due to the lack of several consecutive serum concentration measurements it remains unknown if the serum peak concentration in our patient was in fact even higher.

We have described a case where ILE was successfully used in the treatment of a patient with severe quetiapine poisoning resulting in cardiovascular collapse, which was refractory to vasopressor/inotropic therapy.

Three mechanisms of action that may benefit ILE have been suggested. The first and favored proposed mechanism is the formation of a ‘lipid sink’, sequestering lipophilic toxin within it, thereby reducing toxicity at the affected site. Second, ILE might increase intracellular fatty acid content and thereby increase high energy phosphate content in the intoxicated heart. Third, fatty acids might confer a direct inotropic action by increasing cardiac myocyte calcium levels via action on calcium ion channels.

The ‘lipid’ sink theory might be applicable to any lipophilic toxin, including quetiapine. Much research has focused on the use of ILE in animal models with lipophilic drug intoxications other than local anesthesia. Several comprehensive reviews summarizing the results of animal studies in this area have found consistent evidence of efficacy, dose responsiveness, and plausible ILE mechanisms of action as an antidote for lipophilic toxins.⁶,⁷,¹⁸ A recent review of published human experience of ILE use as an antidote in lipophilic drug poisonings, including several cases of quetiapine overdoses, concludes that ILE should be considered for patients poisoned with lipophilic toxins and exhibiting
cardiovascular instability, despite maximal administration of conventional therapies. The patient presented in this article regained cardiovascular stability after administration of ILE. This observed improvement, although suggestive, failed to definitely identify ILE as the causative factor in the recovery, due to the confounding effect of prior interventions.

This case report of the successful use of ILE represents a contribution to the process of gaining more knowledge about the use of ILE in patients with lipophilic drug poisonings.

Conclusion

Our case demonstrates that ILE may potentially be life-saving in cases of severe quetiapine poisonings. We conclude that ILE should be considered for severe cardiovascular instability resulting from quetiapine poisoning refractory to maximum conventional therapy.

Declaration of interest

The authors report no declarations of interest and declare that they alone are responsible for the content and writing of the paper.

References