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CASE REPORT

Pharmacobezoar Associated Prolonged Clinical Course in a Patient with Immediate Release Quetiapine Overdose

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Abstract

Introduction Quetiapine is available in both immediate-release (IR) and extended-release (XR) formulations. Quetiapine XR overdose is known to cause delayed increase in serum quetiapine concentrations. However, it is not certain whether quetiapine IR overdose would similarly cause a delayed increase in serum quetiapine concentrations.

Case Report A 57-year-old woman with depression who was taking half a tablet of 25 mg quetiapine IR daily was transported to our emergency department with a complaint of disturbance of consciousness 12 h after a quetiapine IR overdose. On arrival, her initial vital signs were heart rate of 116 beats per minute, blood pressure of 77/43 mm Hg, and oxygen saturation of 91% under 10 L oxygen administration. Whole body plain computed tomography showed a large amount of gastric hyperdense content suggesting pharmacobezoar with a volume of 71.2 ml. After treatment with respiratory and circulatory support, gastric lavage was performed. Her disturbance of consciousness persisted until day 5, and she was extubated on day 7. The serum concentrations of quetiapine were 2690 ng/mL at 12 h after overdose, 5940 ng/mL at 40 h, and 350 ng/mL at 124 h after overdose. Serum concentrations of other co-ingestions were all below lethal levels.

Conclusion A massive quetiapine IR overdose with pharmacobezoars can cause a delayed increase in serum quetiapine concentrations.

Keywords Delayed peak of serum concentration · Immediate-release quetiapine · Overdose · Pharmacobezoar · Computed tomography

Introduction

Quetiapine, which is widely used for treatment of depression, bipolar disorders, and schizophrenia, is available in both immediate-release (IR) and extended-release (XR) formulations. Prolonged symptoms of quetiapine XR overdose could be attributed to a delayed increase in serum quetiapine concentrations [1, 2]. This phenomenon may be related to the severity of quetiapine overdose [2]. However, there are few detailed reports on the time course of serum quetiapine concentrations in cases of quetiapine IR overdose. We report a case of an immediate-release quetiapine overdose with pharmacobezoar formation that necessitated prolonged ventilation with a notable delayed peak serum quetiapine concentration of 5,940 ng/mL at 40 h after overdose.

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Case Report

A 57-year-old woman with depression who was taking a half tablet of 25 mg quetiapine IR, 2 tablets of 25 mg trazodone, 2 tablets of 1 mg of risperidone and 1 tablet of 25 mg paroxetine daily was transported to our emergency department with a complaint of disturbance of consciousness for at least 12 h without obvious evidence of an overdose. On arrival, her initial vital signs were heart rate of 116 beats per minute, blood pressure of 77/43 mm Hg, and oxygen saturation of 91% under 10 L oxygen administration. Blood examinations showed no findings that would cause impaired consciousness, and her creatine kinase level was 10,263 IU/L. Plain computed tomography (CT) performed for the evaluation of hypoxia and hypotension showed aspiration pneumonia and large amount of gastric hyperdense context suggesting an overdose of tablets (Fig. 1). Endotracheal intubation using 50 mg of rocuronium and 10 mg of midazolam was performed, followed by norepinephrine continuous infusion to manage persistent hypotension. Gastric lavage was performed without esophagogastroduodenoscopy. She was lavaged with 2 L of tap water using an 18 Fr nasogastric tube, and solid debris of drug formulation was returned. Following gastric lavage, 50 g of activated charcoal was administered. Norepinephrine was used for 3 days and disturbance of consciousness was prolonged for 5 days. After that, her aspiration pneumonia, circulatory status and level of consciousness gradually improved. She was extubated on day 7, and she reported having ingested a full cup of stored medications, primarily quetiapine IR. On day 11, she was transferred to a psychiatric hospital for further care.

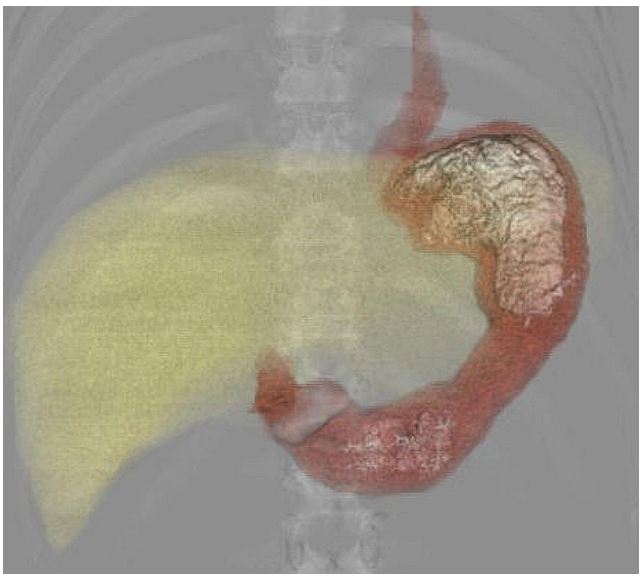

Fig. 1 An abdominal computed tomography at 12 h post-overdose revealed gastric hyperdense context, indicating formation of a gastric pharmacobezoar with a volume of 71.2 ml

Subsequently, examinations using a high-performance liquid chromatograph / tandem mass spectrometer (1260 infinity LC system and 6420 Triple Quad Mass spectrometer (Agilent Technologies, Palo Alto, CA, USA)) revealed that serum concentrations of quetiapine were 2690 ng/mL at 12 h, 5940 ng/mL at 40 h and 350 ng/mL at 124 h after overdose ingestion (Fig. 2). Serum concentrations of trazodone (therapeutic range 0.7 to 1 μg/mL) were 7.25 μg/mL at 12 h, 6.48 μg/mL at 40 h and 1.3 μg/mL at 124 h after overdose ingestion, and the concentrations were all under the lethal level (9 to 15 μg/mL) and decreased linearly [3]. All other co-ingestion drugs including diazepam, levomepromazine, paliperidone, risperidone, paroxetine and zolpidem were detected, with peak serum concentrations not exceeding the upper limit of their respective toxic ranges. Consent for publication of this case was obtained and provided to the journal in accordance with *JMT* policy.

Discussion

A massive overdose of quetiapine IR may result in a delayed peak serum concentration, potentially caused by the formation of gastric pharmacobezoars. In our case, the prolonged symptoms and severity of the quetiapine overdose were likely due to gastric pharmacobezoar formation. In addition, CT may detect the presence of gastric pharmacobezoars, potentially guiding the selection of appropriate gastrointestinal decontamination methods in cases of quetiapine IR overdose.

A delayed peak serum concentration of quetiapine in overdose cases of the IR formulation may be due to the formation of gastric pharmacobezoars. Delayed increase in serum concentrations in cases of a quetiapine XR overdose occasionally occurs and may be attributed to various mechanisms such as pharmacobezoars, redistribution, enterohepatic recirculation and effects of co-ingestions [2, 4]. Among them, formation of pharmacobezoars is considered to play a crucial role in the delayed increase in the serum concentration due to the characteristics of solubility resistance in the gastrointestinal tract and propensity for aggregation [5]. On the other hand, quetiapine IR is absorbed quickly with a mean terminal elimination half-life of only 6 h, and even with an overdose, the half-life is usually less than 24 h [4]. In addition, symptoms of quetiapine IR overdose typically improve within one day [6]. However, in our case, the calculated half-life between the time of peak serum concentration of quetiapine (28 h after admission) and 112 h after admission was 21 h [7], and the central nervous system depression persisted for 5 days. This prolonged symptom may be partly attributed to the fact that serum concentrations of trazodone were at the toxic levels and

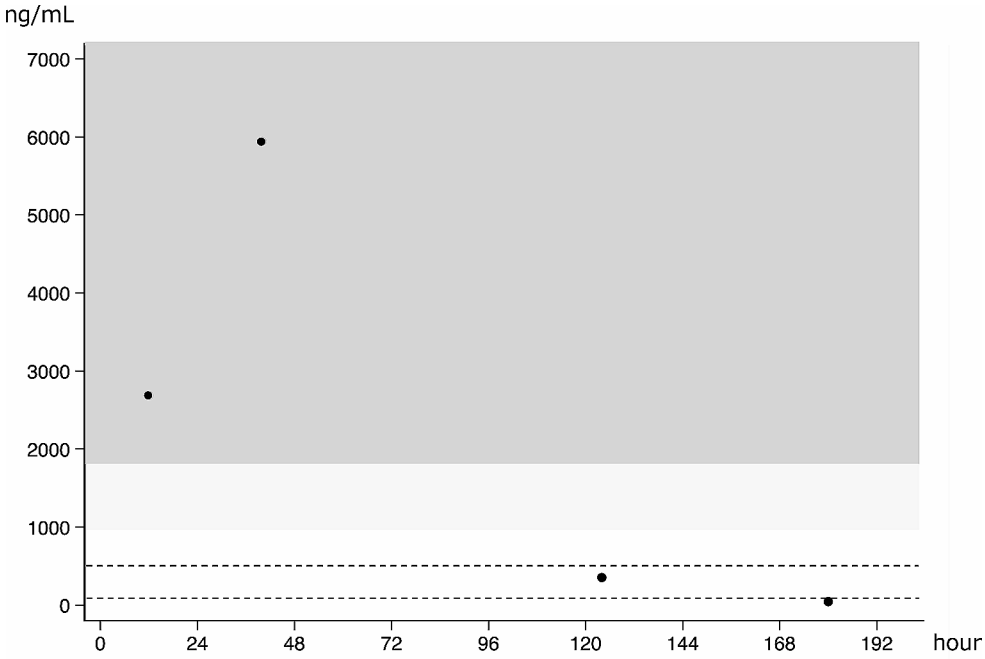

Fig. 2 Time course of serum quetiapine concentrations in our patient with a pharmacobezoar of immediate-release quetiapine. In the figure, the dark gray areas indicate lethal concentrations (> 1800 ng/mL). Light gray areas indicate toxic concentrations (1000 to 1800 ng/mL). The dotted line indicates therapeutic range concentrations (100 to 500 ng/mL)

decreased slowly during the clinical course. It is generally unlikely that cases of a quetiapine IR overdose will exhibit the same changes in serum concentrations as those in cases of a quetiapine XR overdose. However, in our case, a CT scan at 12 h post-overdose revealed formation of a gastric pharmacobezoar. Therefore, as in cases of a quetiapine XR overdose, the serum concentrations in cases of a quetiapine IR overdose with gastric pharmacobezoars would show a characteristic trend of increasing regardless of the time of the patient's arrival. In addition to quetiapine XR formulation, quetiapine IR formulation may also form gastric pharmacobezoars. Physicians should be aware that serum concentrations at admission may not represent peak levels and should remain vigilant for prolonged toxicity throughout the patient's clinical course.

CT may detect the presence of gastric pharmacobezoars and estimate the number of ingested tablets. Various imaging modalities such as simple X-ray and ultrasound have been shown to identify pharmacobezoars [5]. Some reports suggest that even non-contrast CT can detect the presence of a positive radiodense image suggesting ingested drugs in overdose cases [8, 9]. CT has certain limitations compared to simple X-ray and ultrasound, including higher cost and radiation exposure. However, it offers the advantage of evaluating the entire digestive tract, including the esophagus [5]. Although the usefulness of CT may vary depending on the specific circumstances and the type of drug involved, it has the potential to detect gastric pharmacobezoars formed by the accumulation of ingested drug tablets. In addition, focusing on the number of ingested drugs in overdose cases, an in *vitro* study showed that 30 tablets of IR formulation did not create pharmacobezoars [10], and a retrospective study showed that more than 50 tablets of XR formulation created pharmacobezoars, suggesting that larger doses are related to pharmacobezoar formation [11]. In our case, based on the 3D reconstruction of gastric content with CT, the volume of gastric hyperdense content (i.e., higher density than gastric mucosa) was 71.2 ml [8]. The volume of ingested drugs ranged from 84 mm^3 to 208 mm^3, and at least hundreds of tablets were suspected to have been taken. Although co-ingestions such as trazodone, in our case, may influence the formation of gastric pharmacobezoars, even in cases of a quetiapine IR overdose, gastric pharmacobezoar formation may occur in cases of massive ingestion. In practice, information on overdose is often limited in the emergency settings, and it is not fully understood when and under what circumstances the presence of pharmacobezoars should be suspected [5]. However, in patients with unstable vital signs such as ours, it may be necessary to consider the possibility of a pharmacobezoar and investigate their presence using imaging modalities.

The goal of gastrointestinal decontamination for pharmacobezoars is to remove them, thereby reducing the duration and severity of toxicity from ingested drugs. Traditional methods such as gastric lavage, activated charcoal, and whole bowel irrigation are relatively straightforward to perform. However, they cannot be relied upon to completely remove pharmacobezoars [5]. Surgical removal through laparotomy is usually selected in cases of bowel obstruction due to pharmacobezoars; however, this method is often reserved for specific situations, such as overdose cases of certain drugs including iron, due to its invasive nature [5].

Endoscopy is commonly preferred and successfully used to safely remove pharmacobezoars [5]. However, there are potential risks in endoscopic decontamination: injury to the gastrointestinal tract, especially in critically ill patients, and increased absorption and toxicity due to fragmentation of the concretion. In retrospect, given our patient's prolonged unconsciousness, endoscopic gastrointestinal decontamination might have been more effective than blind gastric lavage for gastric pharmacobezoars. Considering the advantages and disadvantages of each method, the development of an effective approach to gastrointestinal decontamination for pharmacobezoars is warranted.

Conclusions

A delayed peak serum concentration of quetiapine was observed in a case of a quetiapine IR overdose. The characteristic changes in serum concentrations were consistent with gastric pharmacobezoar formation. The association in cases of quetiapine IR overdose needs to be further investigated in order to better manage the overdose.

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Declarations

Ethical Approval Consent for publication of this case was obtained and provided to the journal in accordance with *JMT* policy.

Previous Presentation of Data at Meetings or in Abstract Form None declared.

Conflict of interest FI, YO, KH, TI, TC and AN declared that they had no conflict of interest.

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