Gastric pharmacobezoars in quetiapine extended-release overdose: A case series

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Objective. Although extended-release (XR) formulations are recognized to bear some risk of pharmacobezoar formation in overdose, there are no previously documented reports of this phenomenon with quetiapine. We describe nine cases of pharmacobezoar formation in acute quetiapine XR overdose. Methods. Observational case series of all patients who underwent gastroscopy after quetiapine XR overdose, which were reported by physicians to the Swiss Toxicological Information Centre between January 2010 and December 2012, with detailed analysis of cases with documented pharmacobezoar. Results. Gastric pharmacobezoars were detected in 9 out of 19 gastroscopic evaluations performed during the study period. All these patients ingested a large dose of quetiapine XR (10–61 tablets; 6–24.4 g quetiapine). All patients but one also ingested at least one other substance, and in three cases another XR drug formulation. Gastroscopic pharmacobezoar removal was achieved without complications in all patients, but was difficult due to the particular "gelatinous sticky-pasty" consistency of the concretion. The subsequent clinical course was favorable. Conclusions. The possibility of pharmacobezoar formation following a large quetiapine XR overdose should be considered, as this may influence acute patient management. Complete endoscopic pharmacobezoar removal may be a promising approach in selected cases, but further studies are needed to define its role.

Keywords Pharmacobezoar; Bezooar; Quetiapine; Poisoning; Delivery systems; Gastroscopy; Decontamination

Introduction
Pharmacobezoars are concretions of pharmaceutical products such as tablets, suspensions, and insoluble drug delivery systems that form in the gastrointestinal tract, particularly the stomach.1 Although pharmacobezoars appear to be very rare in drug overdose,2–4 the suspicion of their formation may have immediate consequences on patient management, since the effectiveness of whole bowel irrigation, the recommended decontamination procedure in sustained-release drug overdose,2 might be reduced.6 There is some anecdotal evidence that endoscopic removal may be an effective approach in such cases.1,2

Quetiapine is a widely used atypical antipsychotic approved for the treatment of schizophrenia, acute mania, and acute bipolar depression, and as adjuvant in major depressive disorder. Furthermore, it is commonly used off-label for anxiety disorders and sleep disturbances.7,8 With increasing prescription of this drug, reports involving quetiapine poisoning are on the rise, and the clinical picture of quetiapine overdose—with central nervous system depression, sinus tachycardia, ECG abnormalities such as QT-prolongation, mild hypotension, and less frequently seizures, coma, and respiratory depression—has been described in detail.9 In 2007 a sustained-release form of quetiapine was approved by the FDA, Health Canada, and European Union. Although extended-release (XR) formulations are recognized to bear some risk of pharmacobezoar formation in overdose,1 there are no previously documented reports of this phenomenon with quetiapine. However, in two publications of quetiapine overdose, conglomeration has been discussed as a possible explanation for altered pharmacokinetics such as remarkably delayed peak plasma concentrations9 and appearance of a delayed second peak.10 This speculation prompted us to recommend gastroscopic evaluation of two patients who showed delayed deterioration after massive quetiapine XR overdose, with subsequent successful removal of pharmacobezoars in both cases. We describe these two and seven additional cases of quetiapine XR pharmacobezoar formation, which we observed among 19 performed gastroscopic evaluations. Awareness of this phenomenon may be useful in managing patients with potentially severe acute quetiapine XR poisoning.
Materials and methods

This is an observational case series of all patients who underwent gastroscopy after quetiapine XR overdose, the cases of which were reported by physicians to the Swiss Toxicological Information Centre (STIC) between January 2010 and December 2012. All cases of quetiapine XR overdose reported to the STIC during the study period were extracted from the poison center database and reviewed by the investigators. Among these, we identified cases in which gastroscopic evaluation was performed, and those with a documented pharmacobezoar, defined as a concretion of tablets, were further analyzed. Collected data included age, gender, ingested quetiapine dose and number of tablets, coingestants, latency between ingestion and gastroscopy, latency between admission and gastroscopy, gastroscopic findings, signs and symptoms before gastroscopy, clinical course, and length of stay.

Ethics approval was not required due to the nature of the study design according to the regulations of the cantonal ethics committee Zurich, Switzerland (www.kek.zh.ch).

Results

Gastric pharmacobezoars were detected in 9 out of 19 gastroscopic evaluations which were performed among the 239 quetiapine XR overdose cases reported to the STIC during the study period. In six cases with gastroscopic evaluation, numerous apparently sticky tablets were visible in the stomach, and in four cases no tablets were found. Indication for gastroscopy was suspicion of pharmacobezoar formation in two patients with delayed quetiapine toxicity, suspected massive intake of iron medication in combination with quetiapine in one patient, ingestion of a large number of quetiapine tablets in 14 patients, ingestion of two pocket lighters in combination with quetiapine in one patient, and unknown in one case.

All nine patients with documented pharmacobezoars ingested a large dose of quetiapine XR (Seroquel XR): from 10 to 61 tablets corresponding to 6–24.4 g quetiapine. All patients but one also coingested at least one other substance (Table 1). In five cases coingestants were drugs with immediate-release formulation or ethanol, and in three cases also another XR drug formulation (2 venlafaxine XR, 1 paliperidone XR) was involved. Time from ingestion to gastroscopy (known in 7 cases) ranged between 2.25 and 13 h, and latency between admission and gastroscopy between approximately 1 and 16 h.

Details of the gastroscopic findings of the nine patients with documented pharmacobezoars are shown in Table 1 and Figure 1. Gastroscopic pharmacobezoar removal was achieved in all patients, but was difficult and time-consuming due to the particular “gelatinous-sticky-pasty” consistency of the concretion. Coupling direct endoscopic suction with other techniques such as retrieval of parts of the pharmacobezoar with a loop basket or polyip forceps was needed in most cases, and in some patients multiple extraction cycles were required. No mucosal injuries due to these procedures were recorded. Oral activated charcoal was administered to eight patients after endoscopic removal of the pharmacobezoar. Subsequently, none of the patients experienced significant toxicity and the clinical course for each is described in Table 1.

Discussion

We have described a case series of gastric pharmacobezoars documented by gastroscopy in quetiapine XR overdose. Various risk factors for pharmacobezoar formation in the setting of acute drug overdose have been discussed in the literature. The number of ingested tablets seems to play an important role, and this is in accordance with our observation that a large number of tablets was ingested in all patients. Another condition that could favor pharmacobezoar formation is size of the ingested tablets, and this criterion is fulfilled by quetiapine XR tablets which are 17.3 to 19.2 mm long. Accordingly, the formation of pharmacobezoars has been described for tablets of similar length, such as Anafranil™ XR (clomipramine, 13.1 mm), and Isopin™ XR 240 mg (verapamil, 18.6 mm).2,4

The role that particular pharmaceutical excipients play in the formation of bezoars is largely unexplored.1 The gastroscopic descriptions of the concretions in our series as gelatinous, sticky masses of pasty consistency, suggest that the physicochemical properties of drug delivery systems such as the hydroxypropyl methylcellulose (HPMC) matrix, which is contained in quetiapine XR formulations, may play a role. HPMC is a non-toxic polymer widely used as pharmaceutical excipient, especially in controlled-release systems, which can have marked mucocadhesive properties, depending on the ratio and distribution of the methyl and hydroxypropyl substitution as well as the molecular weight.11,12 In contact with water, HPMC swells, forming a gel or colloid of high viscosity,13 and in quetiapine XR tablets this conversion from the dry-glassy mode to the gel mode occurs in 0.5–1.2 h.14 In a comparison of HPMC (subtype E5) with another drug delivery system (water soluble cellulose acetate—WSCA—film coating material) for aspirin tablets, the HPMC-coated tablets were described as tacky and stuck together.15

Based on the position paper of the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists, whole bowel irrigation should be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs, particularly for those patients presenting more than 2 h after drug ingestion.6 However, in case of pharmacobezoar formation, the effectiveness of this decontamination procedure might be reduced.8 Accordingly, in a recent report, the attempt to decontaminate a patient with massive sustained-release clomipramine overdose with gastric lavage combined with administration of polyethylene glycol and oral activated charcoal, proved unsuccessful and failed to prevent further absorption of the active substance. A gradual decrease of plasma drug concentration was observed only after surgical removal of the pharmacobezoar, but the patient’s condition did not improve.16 In another report of a patient with an
<table>
<thead>
<tr>
<th>Patient</th>
<th>Quetiapine XR dose [g], No. of ingested tablets</th>
<th>Coingestant(s)</th>
<th>Latency between ingestion and gastroscopy [h]</th>
<th>Latency between admission and gastroscopy [h]</th>
<th>Gastroscopic findings</th>
<th>Signs and symptoms before gastroscopy</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49 y/o female</td>
<td>18, 60</td>
<td>Lorazepam</td>
<td>unknown</td>
<td>approx. 16</td>
<td>Large conglomerate of white agglutinated tablet material of sticky consistency in the stomach</td>
<td>Symptoms on admission: Somnolence, tachycardia (121 bpm), mild QTc prolongation. 15 h after admission rapid deterioration to GCS 3, generalized convulsion after flumazenil administration</td>
</tr>
<tr>
<td>2 (Figure 1)</td>
<td>41 y/o male</td>
<td>15, 50</td>
<td>Ethanol</td>
<td>13</td>
<td>12</td>
<td>Sticky mass consisting of clumps of expanded agglomerated pills in the stomach</td>
<td>Symptoms on admission: agitation, somnolence, tachycardia (100 bpm). Gradual deterioration to GCS 7 within 12 h Tachycardia (160 bpm)</td>
</tr>
<tr>
<td>3</td>
<td>28 y/o male</td>
<td>24.4, 61</td>
<td>Acetaminophen, Paracetamol XR, Codeine</td>
<td>2.5</td>
<td>1</td>
<td>Numerous large conglomerates of white agglomerated tablets. Some tablets sticking to the stomach mucosa</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>22 y/o male</td>
<td>15, 50</td>
<td>Loroxin oxycodone, Acetylsalicylic acid</td>
<td>approx. 7.5</td>
<td>approx. 1</td>
<td>Large bubblegum-like mass (5 cm diameter) in the stomach, two small conglomerates in the duodenum</td>
<td>Somnolence, tachycardia (101 bpm)</td>
</tr>
<tr>
<td>5</td>
<td>49 y/o male</td>
<td>12, 60</td>
<td>Venlafaxine XR</td>
<td>unknown</td>
<td>2</td>
<td>Numerous conglomerates of agglomerated tablets</td>
<td>Coma (GCS 6), tachycardia (100 bpm), miosis, QTc prolongation Symptoms on admission: Somnolence, tachycardia (160 bpm), hypotension (90/50 mmHg), dyskinesia. Gradual deterioration of vigilance, arterial hypotension requiring brief administration of norepinephrine</td>
</tr>
<tr>
<td>6</td>
<td>28 y/o male</td>
<td>6, 30</td>
<td>Pocket lighters</td>
<td>2.5</td>
<td>1</td>
<td>Numerous large conglomerates of white agglomerated tablets. Some tablets sticking to the stomach mucosa</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>26 y/o female</td>
<td>unknown, 40-60</td>
<td>Mirtazapine, Lorazepam</td>
<td>2.25</td>
<td>1.25</td>
<td>Large conglomerate of tablets and numerous small conglomerates and single tablets in the stomach and the duodenum</td>
<td>Somnolence, tachycardia (150 bpm), intubation because of deterioration of vigilance</td>
</tr>
<tr>
<td>8</td>
<td>26 y/o female</td>
<td>3.10</td>
<td>Lorazepam, Venlafaxine XR, Levomepromazine, Metamizole</td>
<td>3-7</td>
<td>unknown</td>
<td>Sticky cluster of tablets in undigested food</td>
<td>Somnolence, tachycardia (139 bpm), intubation because of deterioration of vigilance</td>
</tr>
<tr>
<td>9</td>
<td>38 y/o male</td>
<td>11.6, 58</td>
<td></td>
<td>5</td>
<td>unknown</td>
<td>Large conglomerate of white agglomerated tablets</td>
<td>Decreased level of consciousness (GCS 10), tachycardia, QTc 480 ms</td>
</tr>
</tbody>
</table>

XR, extended-release; bpm, beats per minute; GCS, Glasgow Coma Scale; QTc, QT interval corrected for heart rate.
XR theophylline pharmacobezoar, rapid fall in serum drug concentration and heart rate was achieved after endoscopic removal of the concretion. In our series, complete endoscopic removal of the pharmacobezoar was successful in all patients, and there was no further clinical deterioration. However, it remains to be demonstrated whether removal decreases morbidity or reduces length of stay. Furthermore, possible adverse effects associated with this procedure cannot be excluded from this limited number of cases.

Conclusions
In conclusion, the possibility of pharmacobezoar formation following a large quetiapine XR overdose should be considered, as this may influence the gastrointestinal decon- tamination strategy. Complete endoscopic pharmacobezoar removal may be a promising approach in selected cases, and further studies are needed to define its role in the man- agement of acute overdose with quetiapine XR, and more generally with drug formulations based on delivery systems with mucoadhesive properties. The manufacturer should take this propensity to form pharmacobezoars under advisement with a view toward developing delivery systems less likely to form bezoars.

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

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References