A case of tolterodine poisoning

一個托特羅定中毒個案

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We present a case of acute tolterodine overdose with anticholinergic toxidrome including drowsiness, confusion and pyrexia. Tolterodine was commonly used in recent years for the treatment of overactive bladder syndrome. Experience with acute tolterodine poisoning was limited. The pharmacology, clinical use and side effects of tolterodine were reviewed. The clinical manifestations, toxicology and management of tolterodine poisoning are discussed. (Hong Kong j.emerg.med. 2010;17:168-172)

本文描述一個急性托特羅定過量的個案，伴有包括昏睡、精神錯亂及發燒等抗膽鹼能中毒綜合徵。近年托特羅定普遍使用於治療膀胱過度活躍綜合徵。托特羅定急性中毒的經驗有限。我們複審托特羅定的藥理學、臨床應用及副作用；及討論托特羅定中毒的臨床徵狀，毒性學及處理。

Keywords: Anticholinergic, Detrol, Detrusitol, overdose, tolterodine

關鍵詞：抗膽鹼能、托特羅、得適妥、過量、托特羅定

Introduction

Tolterodine (Detrusitol®, Detrol®) is one of the most commonly used drugs in recent few years for the treatment of overactive bladder syndrome or detrusor hyperactivity. The clinical experience of this urinary anticholinergic is limited. A case of acute tolterodine overdose is presented and the use of tolterodine is reviewed.

Case presentation

An 82-year-old man was brought to the emergency department by ambulance in March 2008 for intentional overdose of tolterodine one hour ago. He had history of urge incontinence and been prescribed tolterodine 2 mg twice daily by the urologist. He had depression and multiple medical comorbidities including pulmonary silicosis and was put on aspirin, citalopram, fomatidine, folic acid, isosorbide dinitrate, lisinopril, sennatose, paracetamol, frusemide, betaistine and sublingual nitrate. He was found confused by his wife with empty bags of tolterodine at home. The amount of tolterodine ingested was 182 tablets by pill count (2 mg of tolterodine tartrate in each tablet).

He was managed in the resuscitation room. On arrival, his blood pressure was 175/80 mmHg. His pulse rate was 82 beats per minute. He was confused and his Glasgow Coma Scale score was 13/15 (E4V4M5). The body temperature was 38.3 degrees Celsius (tympanic). His respiratory rate was 10 breaths per minute and oxygen saturation by pulse oximetry was 96% while he was put on oxygen through a non-rebreathing mask. The chest auscultation was clear. The abdominal examination revealed hypoactive bowel sound. His
pupils were 5 mm with sluggish response to light. Palpation of the axillary skin showed it was dry. The presence or absence of a palpable bladder was not recorded. Bedside glucose test was 6.8 mmol/L.

The electrocardiogram showed sinus rhythm (Figure 1). The QTc interval as measured by machine was 430 ms. The manual measurement of QT interval was 400 ms and the heart rate was 80 beats per minute, and therefore the QTc by calculation using Bazett’s formula was 462 ms. Chest and abdominal X-rays were taken and were unremarkable. Point-of-care tests of electrolytes and acid-base status were unremarkable. He was given activated charcoal orally but he became increasingly confused and tachypnoeic and could not tolerate oral charcoal. Considering the patient’s poor pulmonary reserve (with known silicosis), relatively large amount of overdose and early presentation, he was intubated with rapid sequence induction using midazolam, suxamethonium and subsequently given a dose of vecuronium. Gastric lavage was performed and activated charcoal was introduced after the lavage. Physostigmine was not considered by the attending emergency physician because of the lack of experience in using physostigmine in tolterodine overdose.

He was transferred to the intensive care unit (ICU) for further supportive management. Serum levels of paracetamol, salicylate and ethanol were normal. Serial blood tests for baseline and electrolytes were monitored during the hospital stay, as shown in Table 1.

Hyponatremia was noted since day 3 after admission. The thyroid function test and spot cortisol were normal. Serum and urine osmolality were unremarkable. A brief period of hyperamylasemia was present in the first two days, and subsequently returned to normal. There was no report of abdominal pain.

The patient was successfully extubated two days after the ICU admission. Serum and urine toxicology screen revealed caffeine but tolterodine assay was not available in the laboratory. He was subsequently transferred back to the medical ward. There was flare up of silicosis during his stay in the medical ward and he was transferred to a mental hospital 16 days after admission.

**Discussion**

Tolterodine tartrate (Detrusitol®, Detrol®) is one of the most commonly used drugs in the recent few years for the treatment of overactive bladder syndrome or detrusor hyperactivity. It is a synthetic tertiary amine with antimuscarinic effect (Figure 2). Although it is commonly claimed to be more selective on the urinary

![Figure 1. Electrocardiogram of the patient.](image-url)
system, it is a non-selective competitive muscarinic antagonist by receptor affinity. However, it had greater biologic effect on the bladder in vivo. The relative selectivity of action will be lost in case of acute overdose. In the literature there has been no case report of tolterodine poisoning due to single oral overdose, while acute anticholinergic poisoning of a prototype urinary antispasmodic, oxybutynin, was well studied and reported. The pharmacokinetic and pharmacodynamic properties of tolterodine are relatively well studied, while toxicokinetics and toxicodynamics in conditions of overdose remain uncertain. In therapeutic doses, tolterodine is well absorbed (77%) following oral ingestion. It undergoes extensive first-pass effect with variable bioavailability. The volume of distribution of tolterodine following the administration of a 1.28 mg intravenous dose is 113±26.7 L (physician prescribing information of tolterodine tartrate, Pfizer). It is highly protein bound (96.2%). It is extensively metabolised in liver to an active metabolite 5-hydroxymethyltolterodine, and the metabolites are excreted in urine. The major metabolic pathway is catalysed by the CYP2D6 system in the liver. Poor metabolisers are associated with cytochrome P450 2D6 polymorphism. The half life of tolterodine is 1.9 to 3.7 hours while the half life of 5-hydroxymethyltolterodine is 2.9 to 3.1 hours. Despite the influence of CYP2D6 polymorphism on the metabolism of tolterodine, this does not appear to be of great pharmacodynamic importance. The adverse drug reactions of tolterodine under therapeutic use include those of anticholinergic side
effects (xerophthalmia, blurring of vision, xerostomia, tachycardia, constipation, dyspepsia, dizziness, somnolence, anxiety, fatigue and impaired cognition).

With patch-clamp electrophysiology, tolterodine was found to be a potent antagonist of the human ether-a-go-go-related gene (HERG) potassium channel.\textsuperscript{6} Drugs that block HERG/IKr with high affinity are often associated with QT prolongation on the electrocardiogram and the development of torsade de pointes. Indeed, HERG channel affinity is now widely used both to predict and to explain drug-induced QT prolongation and ventricular arrhythmia. Nevertheless, clinically significant prolongation of QT interval and torsade de pointes have neither been reported in controlled clinical trials nor in post-marketing surveillance of tolterodine. One of the possible explanations is the high protein binding of tolterodine, with low free plasma level that is simply not high enough to produce QT-prolonging effects.\textsuperscript{6,7} Still electrocardiographic studies of poor metabolisers of the drug (cytochrome P450 2D6 polymorphism) with high free plasma levels reported no prolongation of the QT interval.\textsuperscript{6} One observation and explanation was the effect on cardiac L-type calcium channel by tolterodine. Tolterodine was found to be an effective blocker of cardiac L-type calcium channel, which could account for the lack of QT prolongation even with high free plasma level.\textsuperscript{6,7} This effect is also seen with verapamil.\textsuperscript{8} It is interesting that verapamil and tolterodine represent the rare examples in which potent blockage of the HERG channel in vitro does not directly translate into clinically significant QT prolongation and arrhythmias (that means false positivity in the HERG assay).

Although no significant prolongation of QT interval and ventricular arrhythmias have been reported to be associated with tolterodine, caution should be raised in patients with congenital long QT syndrome and prolonged QT interval (physician prescribing information of tolterodine tartrate, Pfizer). Contraindications in clinical use include uncontrolled narrow-angle glaucoma, gastric and urinary retention, which are associated with the anticholinergic properties.

In our case, hyponatremia was noted from day 3 to day 6. In the literature there were two case reports about tolterodine associated hyponatremia under therapeutic dose.\textsuperscript{9,10} Hyponatremia was reproducible with rechallenge in both cases. However, the occurrence of hyponatremia is uncertain in the setting of acute overdose.

Another interesting reported association is tolterodine-associated acute mixed liver injury under therapeutic use.\textsuperscript{11} It was proposed by Schlienger that it might be an organ manifestation of tolterodine-induced hypersensitivity syndrome. However, this has not been reported in overdose. In our patient, the bilirubin, liver parenchymal and ductal enzymes remained grossly normal during his hospital stay.

A brief period of hyperamylasemia was noted in our case. Hyperamylasemia and acute pancreatitis has been well reported in anticholinesterase poisoning.\textsuperscript{12} Muscarinic receptors M1 and M3 were found in the acinar cells of the pancreas.\textsuperscript{13,14} Anticholinergics, such as pirenzepine, has been used as part of the treatment for acute pancreatitis. The proposed mechanism was spasmylic effect on the sphincter of Oddi, and reduction of vagally mediated pancreatic secretion by the anticholinergic property.\textsuperscript{15,16} However, this clinical use is not universal in the world. For anticholinergic overdose, no case reports or discussions of hyperamylasemia and pancreatitis could be found in the literature. In our patient, there was no ultrasonography or other imaging performed for radiologic evidence of pancreatitis and assessment of the biliary tree. The association of hyperamylasemia and tolterodine overdose cannot be confirmed.

The management of patients with tolterodine overdose depends on the clinical identification of the anticholinergic toxidrome. Determination of tolterodine and 5-hydroxymethyltolterodine could be done by gas chromatography-mass spectrometry,\textsuperscript{17,18} but it will not affect the acute management. The management should be focused on supportive measures and consideration of gastrointestinal decontamination.
For central neurological anticholinergic effects, we may consider using physostigmine, which may avert intubation and confirm the diagnosis of the anticholinergic toxidrome.

**Conclusion**

We report a case of tolterodine poisoning presenting with the classical anticholinergic toxidrome. Other observations included brief periods of hyperamylasemia and hyponatremia. We have reviewed other interesting phenomena associated with tolterodine that were reported in the literature, which include acute liver injury, hyponatremia and potential effect on the QT interval. The basic principle of the management of anticholinergic overdose applies in tolterodine poisoning.

**References**