

Paradoxical and severe hypotension in response to adrenaline infusions in massive quetiapine overdose

David J Hawkins and Peter Unwin

Atypical antipsychotics (quetiapine, olanzapine, risperidone and clozapine) were introduced in Australia in the mid-1990s. Their efficacy in treating both the positive and negative symptoms of schizophrenia, coupled with the infrequency of disabling extra-pyramidal side effects, have seen this class of drug replace the older, traditional antipsychotics as first-line pharmacotherapy. Commensurate with this change in prescribing practice has been a significant increase in the frequency of patients with severe overdose with these agents presenting to emergency departments (EDs) and intensive care units. We describe three patients with massive quetiapine overdose associated with significant hypotension resistant to fluid resuscitation. In each case, adrenaline infusions were begun by (different) senior clinicians, resulting in considerable worsening of haemodynamic status. Blood pressure subsequently returned to normal with the substitution of noradrenaline for adrenaline. We believe this interaction is not well described in the medical literature and is not widely familiar to critical care clinicians. Here, we discuss the pharmacology of quetiapine and the literature on quetiapine overdose.

Clinical records

Patient 1

A 59-year-old woman with schizophrenia presented 2 hours after intentionally ingesting quetiapine (20 g). On arrival in the ED, she was drowsy, with a Glasgow Coma Score (GCS) of 14/15, tachycardia (heart rate, 125 beats/min), and hypotension (blood pressure, 82/51 mmHg). The only notable finding on electrocardiogram (ECG) was sinus tachycardia; PR, QRS and QTc intervals were normal. She was treated with normal 0.9% saline (1000 mL) intravenously (IV), with some increase in blood pressure (90/60 mmHg).

About an hour later, her GCS fell to 11/15. Tracheal intubation was performed electively for airway protection, with midazolam (5 mg IV), fentanyl (200 µg IV) and suxamethonium (100 mg IV). An infusion of morphine and midazolam was titrated to 5 mg/h of each to provide adequate sedation.

After intubation, the patient's blood pressure decreased, with systolic blood pressure (SBP) falling to 70 mmHg, but no concurrent ECG changes. Hypotension persisted despite rapid IV infusion of 3000 mL saline. Central venous access was obtained, and an adrenaline infusion was begun by the treating ED consultant, initially at 5 µg/min, rapidly escalating

ABSTRACT

Atypical antipsychotics (quetiapine, olanzapine, risperidone and clozapine) are increasingly prescribed in Australia, and emergency departments report growing rates of overdose of these agents. As these drugs are comparatively new, the spectrum of toxicity may be unfamiliar to critical care physicians. Severe hypotension is a recognised consequence of quetiapine poisoning.

We describe three patients with massive quetiapine overdose who developed significant hypotension resistant to fluid resuscitation. In each case, blood pressure fell dramatically after commencement of adrenaline infusions. Haemodynamic stability was restored when noradrenaline was substituted for adrenaline.

The pharmacodynamics of quetiapine and the literature on overdose are reviewed. We present these cases to broaden the knowledge of physicians treating quetiapine overdose and to publicise the potential deleterious interaction with adrenaline. We recommend use of noradrenaline in preference to adrenaline in pharmacological management of shock in these patients.

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to 20 µg/min. It was apparent that increases in adrenaline were associated with paradoxical falls in blood pressure, with the SBP ultimately reaching a nadir of 53 mmHg.

After consultation with the toxicology service, adrenaline was withdrawn, and noradrenaline was begun, with dose escalation to 15 µg/min. SBP rose to 120 mmHg, with adequate urine output and normal acid–base status.

The patient was subsequently admitted to the ICU. Noradrenaline was weaned over 6 hours, with her haemodynamic status remaining stable. She was extubated the following day and discharged to a psychiatric ward.

Patient 2

A 38-year-old man with bipolar affective disorder presented 2 hours after impulsively ingesting quetiapine (about 15 g). On arrival, his GCS was 3/15, and he required assisted ventilation via a laryngeal mask airway inserted by the transferring paramedics. Haemodynamic observations revealed a heart rate of 115 beats/min in sinus rhythm, and

blood pressure of 80/50 mmHg. The ECG confirmed sinus tachycardia but appeared otherwise normal. The airway was secured with an endotracheal tube without additional drug administration, and positive pressure ventilation was begun. Sedation was continued with an infusion of morphine and midazolam (5 mg/h of each). After volume resuscitation, SBP increased to 110 mmHg, although heart rate remained unchanged.

Two hours after the patient's arrival, his blood pressure fell to 70/40 mmHg. Hypotension persisted despite rapid volume expansion with 2000 mL 0.9% saline IV. An adrenaline infusion was begun and increased incrementally to 20 µg/min, although blood pressure continued to fall. The ECG remained unchanged. Noradrenaline at 10 µg/min was substituted for adrenaline, resulting in a dramatic rise in SBP to 120–140 mmHg.

Noradrenaline was weaned over the 12 hours after ICU admission. The patient was extubated the following day, and discharged home with psychiatric follow-up.

Patient 3

A 27-year-old man presented to the ED following intentional ingestion of quetiapine (17 g). His GCS was 7/15 on admission, and deteriorated over the ensuing hour to 4/15, necessitating tracheal intubation (with fentanyl 100 µg IV, propofol 80 mg IV, and suxamethonium 100 mg IV) and mechanical ventilation. Sedation was maintained with morphine and midazolam (8 mg/h of each).

Thirty minutes after intubation, his heart rate was 110 beats/min in sinus rhythm, and blood pressure was 95/70 mmHg, rising to 105/80 mmHg after infusion of 1500 mL 0.9% saline IV. Over the following 3 hours, the SBP fell progressively to 70 mmHg despite the further administration of 2000 mL crystalloid IV and the exclusion of any other reversible cause of hypotension. The ECG was unexceptional, except for sinus tachycardia.

A femoral venous line was inserted, and adrenaline was administered, initially at a dose of 5 µg/min IV, increasing to 10 µg/min IV. SBP fell to 55 mmHg after the increase in infusion rate. Adrenaline was withdrawn, and noradrenaline was introduced, initially at 5 µg/min. SBP rapidly rose to 120 mmHg.

Haemodynamic support with noradrenaline was maintained at 5 µg/min for the next 14 hours and then weaned. The patient was extubated at 24 hours and made an uneventful recovery.

Discussion

This case series illustrates a severe adverse and paradoxical reaction to an adrenaline infusion used to treat hypotension refractory to fluid resuscitation in three cases of substantial quetiapine overdose. The haemodynamic status of all three

patients improved dramatically when noradrenaline was substituted for adrenaline. This paradoxical hypotensive response does not appear commonly known, as the three patients were managed by different experienced ICU/ED physicians, and none was aware of the potential interaction. Additionally, MIMS does not refer to pharmacological support of hypotension in quetiapine overdose.¹

In pure quetiapine overdose, the most common manifestations are reported as drowsiness, tachycardia, hypotension and coma.² Formal management guidelines for atypical antipsychotic overdose do not exist, but should follow the basic tenets of airway protection and cardiorespiratory support. There are insufficient data to refute or confirm the efficacy of activated charcoal. Hypotension, which is mediated by α_1 -adrenoceptor antagonism, is relatively uncommon in overdose, being reported in 6%–18% of toxic ingestions.^{3–5} However, it would be expected to be more common in patients requiring intubation and mechanical ventilation.

In our series, adrenaline was chosen as the initial agent of pharmacological support when fluid loading failed to correct the hypotension. This decision reflected the familiarity and experience of the treating specialists. While the preference for adrenaline over noradrenaline proved flawed in hindsight, a recent Cochrane review established that no high-quality evidence exists to assist the clinician in the choice of catecholamine for fluid-resistant shock.⁶ Published studies comparing vasoactive drugs have been criticised for poor design and small patient numbers.^{6,7} Additionally, these trials failed to prove superiority of one catecholamine over another, either alone or in combination. Thus, the choice of vasoactive agent is usually determined by the personal preference of the treating specialist.

Noradrenaline and adrenaline have similar β_1 actions on the heart and similar potency at α receptors. However, noradrenaline, in contrast to adrenaline, has relatively little activity at β_2 -adrenoceptors, which mediate vascular smooth muscle relaxation and decrease peripheral resistance. Consequently, noradrenaline increases peripheral resistance to a greater degree than does adrenaline. Compensatory vagal reflexes tend to overcome the positive chronotropic actions of noradrenaline on the myocardium, although positive inotropy is preserved.⁸

Based on the pharmacodynamic characteristics of quetiapine (specifically its α_1 antagonism), adrenaline would potentially aggravate haemodynamic compromise, via enhanced chronotropy and associated reduction in left ventricular filling time, compounded by β_2 -stimulated vasodilation. In contrast, the α_1 -vasoconstrictive action of noradrenaline, unopposed by vasodilatory β_2 action, would theoretically render it a superior agent for reversing hypotension after overdose.

The literature regarding the specific management of hypotension secondary to quetiapine overdose is sparse and

consists solely of case reports and expert opinion. Several reports describe hypotension related to quetiapine toxicity resolving only with volume resuscitation.^{9,10} Case series of quetiapine poisonings record the (infrequent) use of noradrenaline to support blood pressure, but do not record outcomes apart from survival. Expert reviews of quetiapine pharmacodynamics and toxicity concur that noradrenaline should be the pharmacotherapeutic agent of choice.^{3,11}

In essence, this series demonstrates the physiological effects of unbalanced β -stimulation overwhelming α -adrenergic activity. Lessons from the above cases can be applied to other situations, including overdose with other drugs that antagonise α_1 -adrenoceptors, such as tricyclic antidepressants (TCAs). Cardiac toxicity and hypotension in TCA overdose are mediated by several mechanisms, including α_1 -adrenoceptor blockade. While trial data are lacking, expert consensus recommends that hypotension after TCA overdose that persists after volume loading and alkalinisation be treated with noradrenaline rather than adrenaline.¹² Similarly, hypotension after antihistamine and phenothiazine overdose is also in part mediated by excessive α_1 blockade, suggesting that noradrenaline would be superior to adrenaline for pharmacological management.

The hyperadrenergic state in patients with pheochromocytoma illustrates the interplay between excessive β activity and the *therapeutic* role of α -blockade in preventing life-threatening hypertensive crises and controlling blood pressure preoperatively. The non-competitive α -antagonist phenoxybenzamine is traditionally the preferred agent for blood pressure control.¹³ The dose is titrated against several variables, including supine blood pressure and the degree of orthostatic hypotension (which results from unopposed β_2 action from secreted catecholamines and α_1 blockade secondary to phenoxybenzamine). Longstanding vasoconstriction leading to compensatory contraction of the blood volume also contributes to the development of postural hypotension. Postoperatively, the pathophysiology is reversed, with hypotension commonly occurring because of the reduced adrenergic stimulation following the significant reduction of circulating catecholamines, in the face of persisting preoperative α blockade and uncorrected hypovolaemia.

Lastly, intensivists should consider the possibility of hypertrophic obstructive cardiomyopathy (HOCM) in patients with hypotension exacerbated by escalating doses of adrenaline. Increasing cardiac β_1 stimulation worsens dynamic outflow obstruction by increasing contact between the anterior mitral leaflet and the interventricular septum during systole.¹⁴ Hypotension is exacerbated by β_2 dilatory action on the peripheral vasculature in the face of a fixed stroke volume. As in the adrenaline/quetiapine cases, blood pressure falls because β activity overwhelms compensatory α -adrenergic action. In the critically ill patient with HOCM requiring haemodynamic support, vasoconstrictors and volume loading are recommended instead of inotropes.¹⁴

Conclusions

Australia has had a decade's experience with typical antipsychotics, and they now account for most antipsychotic overdoses. It is important for critical care physicians to become familiar with their toxicology.

Central nervous system depression, sinus tachycardia and hypotension are the most frequent consequences of overdose. Death is infrequent, and adequate supportive care should prevent significant morbidity or mortality.

Profound hypotension resistant to volume resuscitation is a relatively uncommon complication of quetiapine poisoning. However, when it occurs, the experience from our case series and review of quetiapine pharmacodynamics suggests that noradrenaline should be the vasoactive agent of choice.

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References

- 1 eMIMS. Sydney: CMPMedica Australia, 2008. <http://www.mims.com.au> (accessed Jun 2008).
- 2 Litovitz TL, Klein-Schwartz W, Caravati EM, et al. 1998 annual report of the American Association of Poison Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 1999; 17: 435-87.
- 3 Burns MJ. The pharmacology and toxicology of atypical antipsychotic agents. *J Toxicol Clin Toxicol* 2001; 39: 1-14.
- 4 Ngo A, Ciranni M, Olsen KR. Acute quetiapine overdose in adults: a 5 year retrospective case series. *Ann Emerg Med* 2008; Apr 21. [Epub ahead of print.]
- 5 Balit CR, Isbister GK, Hackett LP, Whyte IM. Quetiapine poisoning: a case series. *Ann Emerg Med* 2003; 42: 751-8.
- 6 Mulner M, Urbanek B, Havel C, et al. Vasopressors for shock. *Cochrane Database Syst Rev* 2004; (3): CD003709.
- 7 Myburgh JA. Catecholamines for shock: the quest for high-quality evidence. *Crit Care Resusc* 2007; 9: 352-6.
- 8 Hoffman BB. Adrenoceptor activating and other sympathomimetic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 8th ed. International edition. Lange Medical Books/McGraw-Hill, 2001: 130.
- 9 Hustey FM. Acute quetiapine poisoning. *J Emerg Med* 1999; 17: 995-7.
- 10 Pollak PT, Zbuk K. Quetiapine fumarate overdose: clinical and pharmacokinetic lessons from extreme conditions. *Clin Pharmacol Ther* 2000; 68: 92-7.
- 11 Trenton AJ, Currier GW, Zwemer FL. Fatalities associated with therapeutic use and overdose of atypical antipsychotics. *CNS Drugs* 2003; 17: 307-24.
- 12 Kerr GW, McGuffie AC, Wilkie S. Tricyclic antidepressant overdose: a review. *Emerg Med J* 2001; 18: 236-41.
- 13 Lenders JWM, Eisenhofer G, Mannelli M, Pacak C. Pheochromocytoma. *Lancet* 2005; 366: 665-75.
- 14 Nishimura RA, Holmes DR. Hypertrophic obstructive cardiomyopathy. *N Engl J Med* 2004; 350: 1320-7. □