CASE REPORT

Vasopressor therapy in atypical antipsychotic overdose

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Hypotension is a common presentation following an overdose of quetiapine. Adrenaline is often used as the vasopressor of choice for hypotension not responding to intravenous fluids. We present a case of quetiapine overdose with hypotension unresponsive to high-dose adrenaline. The patient was commenced on noradrenaline and made a full recovery. We highlight learning points about vasopressor therapy for atypical antipsychoptic overdose. Quetiapine-induced hypotension is thought to be mediated by α-receptor antagonism. Adrenaline is unlikely to improve blood pressure, as it is an agonist at both α- and β-receptors. Alpha-2- and β-agonism can reduce sympathetic outflow and cause vasodilation, respectively, further exacerbating the hypotension. Noradrenaline is the preferred vasopressor of choice for hypotension caused by quetiapine overdose, as it has less affinity for α- and β-receptors, but maintains α-receptor agonism. Drugs with a similar mechanism of inducing hypotension should also be treated with noradrenaline as the vasopressor of choice.


Mortality due to intentional self-harm in South Africa (SA) constitutes 0.1% of all-cause mortality and 0.8% of non-natural deaths.¹ Data on admissions to intensive care units (ICUs) in SA following overdose (OD) are sparse. A 2014 study conducted at Frere Hospital in East London, SA, found that 5.6% of ICU admissions were related to OD, constituting 25% of all medically related ICU admissions.² An Australian study reported an ICU admission rate between 13% and 22% following an OD.³ In the USA, 1% of emergency admissions are due to OD, with ~25% of these patients requiring ICU admission.⁴ In the 2018 Annual Report of the American Association of Poison Control Centers’ National Poison Data System, antipsychotics remain the second-largest class of drugs – after analgesics – involved in ODs in adults.⁵

Atypical antipsychotics such as quetiapine, olanzapine, clozapine and risperidone exert antagonist activity on serotonin and dopamine receptors, warranting their use in bipolar disorder and schizophrenia.⁶ In addition, they display off-target binding to α-adrenergic receptors that may lead to vasodilation and lowered blood pressure.⁷ Quetiapine has a greater preponderance to cause hypotension than most antipsychotics.⁸ A systematic review of cardiovascular toxicity associated with atypical antipsychotic OD noted tachycardia, hypotension and prolonged QRS intervals as common presentations, with hypotension recorded in up to 42% of patients presenting with an OD of quetiapine only.⁹ Deaths from quetiapine OD were estimated to be in the range of 31.3 per million prescriptions in England and Wales between 1993 and 2002.¹⁰ A more recent analysis in Australia between 2006 and 2016 estimated death as a direct consequence of quetiapine OD to be ~1.2% in cases where quetiapine was detected post mortem.¹¹ Quetiapine was also implicated as contributory to death in 37.4% of polypharmacy ODs in the same analysis.¹² Although some international data are available, there remains a paucity of data on quetiapine OD in the SA setting. Hypotension is a common and often challenging presentation in patients who have taken an OD of commonly prescribed medications such as antipsychotics, tricyclic antidepressants, beta-blockers or calcium channel blockers.¹³ In an SA study, hypotension was reported as a frequent indication for ICU admission in tricyclic antidepressant OD.¹⁴ Haemodynamic monitoring has been recorded as the second most common reason for ICU admission following a depressed level of consciousness requiring intubation.¹⁵ Previous reports have advocated against the use of adrenaline to manage hypotension resistant to intravenous fluids (IVF) in quetiapine OD.¹⁶ By virtue of its mechanism of action, adrenaline use in the setting of quetiapine OD further lowers the blood pressure.¹⁷ Adrenaline is a readily available and cost-effective vasopressor included in the essential medicines list for SA. However, adrenaline may not be an effective or pharmacologically appropriate vasopressor in all cases of OD-associated hypotension. We report a case of a patient who took an OD of quetiapine, an atypical antipsychotic, and presented with significant hypotension unresponsive to adrenaline.

Case report

A 19-year-old woman was brought to the emergency unit by her relatives, following a reported OD of an unknown amount of her prescription quetiapine tablets. Her notable past medical history included major depressive disorder, generalised anxiety disorder with borderline personality traits, and regular cannabis use. No co-ingestants were reported.

On initial assessment, her vital signs were within normal limits: blood pressure (BP) 116/69 mmHg, heart rate 70 bpm, afebrile, respiratory rate 20 breaths per minute, and oxygen saturation 97% on room air. However, owing to her depressed level of consciousness (Glasgow Coma Scale 7/15) and subsequent inability to protect her airway, rapid-sequence intubation was performed with succinylcholine and ketamine. Her electrocardiogram showed sinus tachycardia only, with no other abnormalities such as a prolonged QT interval or a widened QRS complex. Her baseline blood results (full
blood count, liver function tests, glucose, and urea, creatinine and electrolytes) were unremarkable.

Six hours after ingestion, the patient developed hypotension with BP 76/37 mmHg and mean arterial pressure (MAP) 50 mmHg. The treating doctor initiated an adrenaline infusion: 20 mg of 1:1 000 adrenaline diluted in 200 mL normal saline, running at 10 mL/h. The infusion was titrated up to 28 mL/h in an attempt to improve her BP, which did not increase above 84/45 mmHg with MAP 58 mmHg. The Poisons Information Helpline of the Western Cape was contacted regarding the next appropriate management steps, and advised the attending clinician to commence noradrenaline as the preferred vasopressor of choice in quetiapine OD. The patient’s BP subsequently increased to 98/42 mmHg with MAP 64 mmHg. She remained stable with MAP >60 mmHg. Noradrenaline was weaned and eventually stopped 28 hours after initiation. The patient was extubated shortly thereafter and made a full recovery.

Discussion

In the case presented, our patient had profound hypotension following quetiapine OD. There was inadequate blood pressure response on adrenaline. After commencement of noradrenaline, the blood pressure improved significantly and the patient made a full recovery.

Quetiapine is an atypical antipsychotic drug. It is primarily an antagonist of 5HT2 and D2-receptors, where it exerts its antipsychotic and mood-stabilising effects.[13] It also has antagonistic effects on histamine (H1) and adrenergic (α1 and α2) receptors, although it has a higher potency at α1 than α2-receptors.[14] Potent antagonism of α1-receptors is purported to cause the hypotension seen in OD.[15] Quetiapine OD in QD is also more likely than the other atypical antipsychotics to produce significant clinical effects such as coma, respiratory depression or hypotension.[16]

The incidence of hypotension may be as high as 18% in patients with quetiapine OD,[17] and pharmacological management begins with the administration of IVF, followed by vaspressors if IVF fails.[18] In the SA context, adrenaline is frequently used as the first-line vasopressor of choice by attending doctors. However, in quetiapine OD, noradrenaline is recommended as the vasopressor of choice in the management of hypotension.[19] The rationale for the preference of noradrenaline over adrenaline in managing such patients is based primarily on their receptor propensities. Adrenaline has both β1- and β2-receptor agonist activity in addition to its α1- and α2-receptor agonism.[20] Quetiapine OD causes hypotension by potent antagonism of α2-receptors, with adrenaline displaying suboptimal vasoconstriction owing to not fully displacing quetiapine from the α1-receptor. The simultaneous stimulation of presynaptic α2-receptors in addition to β-receptors by adrenaline reduce sympathetic outflow by decreasing noradrenaline release from the sympathetic nerve endings, and paradoxical vascular smooth-muscle relaxation and vasodilation, respectively,[19,20] thereby decreasing systemic vascular resistance and further lowering blood pressure.[21] The net effect is that the hypotension is unlikely to improve and may even deteriorate following the administration of adrenaline in these patients. In comparison with adrenaline, noradrenaline has potent α1-receptor activity and less affinity for β-receptors.[22] The vasoconstriction mediated by noradrenaline (α1-agonism) is therefore not counteracted by peripheral vasodilatation (β2-agonism), and the adverse effect of a quetiapine OD on blood pressure is not augmented.[19,22]

Other atypical antipsychotics commonly used in SA, such as olanzapine, clozapine and risperidone, may cause hypotension in OD. Similar to quetiapine, olanzapine, clozapine and risperidone mediate hypotension by α1-adrenergic antagonism.[23] The use of vaspressors with β1-receptor agonism could therefore also result in refractory hypotension. Tricyclic antidepressants (TCAs) may also cause hypotension in OD by α1-adrenergic antagonism, and therefore noradrenaline may likewise be a more appropriate alternative in these patients.[24,25] Noradrenaline has also been shown to be a better vasopressor than dopamine in TCA-induced hypotension.[26] Dopamine exerts some of its effects through the release of catecholamines, which may be depleted in OD states.[26] It may therefore not be a suitable drug to treat refractory hypotension in these ODs. On the contrary, in beta-blocker OD, unopposed β1- or α1-receptor stimulation is potentially hazardous, and adrenaline is the preferred drug of choice as it possesses both α1- and β1-receptor agonism.[27] Noradrenaline is currently only accessible via Section 21 approval in SA. Selected hospitals should consider having limited stock available to facilitate prompt access to noradrenaline in cases of significant quetiapine OD.

Conclusions

Drug ODs are common presentations to emergency units globally, and SA is no exception. Knowledge of the specific mechanisms of action of these drugs, as well as those of the vaspressors available to the attending doctor, is of paramount importance and will ensure the appropriate selection of vasopressors when indicated and mitigate potential iatrogenic complications. While adrenaline is often the first-line vasopressor in hypotension not responding to IVF, the recommended vasopressor of choice for quetiapine OD is noradrenaline.

Teaching points

- Quetiapine OD commonly presents with hypotension as a result of α1-adrenergic receptor antagonism.
- Adrenaline is commonly used as a first-line vasopressor in hypotension unresponsive to IVF. However, in quetiapine OD, adrenaline may worsen blood pressure owing to presynaptic α1- and β2-adrenergic receptor agonism, resulting in reduced sympathetic outflow and vasodilatation, respectively.
- Noradrenaline is the preferred vasopressor in quetiapine OD owing to its potent agonism at α1-adrenergic receptors and negligible effects at α2- and β1-receptors.
- In SA, noradrenaline is accessed via Section 21 approval. Selected hospitals should consider having stock available to facilitate prompt access to noradrenaline in cases of significant quetiapine OD.

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