Dolasetron overdose resulting in prolonged QTc interval and severe hypotension: a case report and literature review

Martin Rochford, Thomas J Kiernan, Amjed Aziz

Dolasetron (Anzemet) overdose is uncommon, and, to our knowledge, this is the only case report of an intentional overdose. Dolasetron (dolasetron mesylate) is a selective 5-hydroxytryptamine 3 antagonist derived from pseudopelletierine, and is used in the prevention and treatment of nausea and vomiting. Transient and asymptomatic ECG changes, including QRS widening and PR and QTc prolongation, have been reported in therapeutic doses. The case of a 21-year-old woman who presented after an intentional overdose of 10×200 mg dolasetron tablets resulting in prolongation of the QTc interval and severe hypotension is reported here. Management of hypotension included intravenous fluid resuscitation and norepinephrine infusion with invasive monitoring in a high dependency unit. Sodium cardiac channel block contributes to cardiotoxicity observed in dolasetron overdose. Sodium bicarbonate was used in an attempt to reduce cardiac sodium channel block, although we observed no apparent benefit. As dolasetron becomes more commonly used in the outpatient setting, both doctors and patients need to be aware of the dangers of dolasetron in toxic doses. The pharmacology and toxicology of dolasetron are discussed.

Dolasetron (dolasetron mesylate) is a selective 5-hydroxytryptamine 3 antagonist used in the prevention and treatment of nausea and vomiting (Company datasheet, ANZEMET®Tablets (dolasetron mesylate) Aventis Pharmaceuticals, Kansas City, Missouri, USA, June 2005). The recommended oral dosage is 200 mg daily.

A 21-year-old woman presented to the emergency department at 19:00 h, 3 h after an intentional overdose of 10×200 mg dolasetron tablets. She had

consumed alcohol 12 h previously and taken a half tablet of ecstasy (3,4-methylenedioxymethamphetamine) and an amphetamine tablet the previous night. On arrival she was drowsy, with a Glasgow Coma Scale of 13/15, respiratory rate of 30/min, a regular pulse of 72 beats/min and blood pressure of 64/30 mm Hg. Pupils were of 4 mm size, equal and reactive, and she was neurologically intact. ECG showed a sinus rhythm of 70 beats/min with first-degree heart block, non-specific

intraventricular conduction delay and QTc interval of 611 ms (normal value: 460 ms in men, 470 ms in women), as calculated by Bazett's formula (fig 1).¹ Initial laboratory results, including venous blood gas analysis, were normal (table 1), except for a calcium level of 2.09 mmol/l (normal range 2.25–2.58 mmol/l).

The patient's Glasgow Coma Scale returned to normal after a 1 litre fluid bolus, but she remained hypotensive. Arterial and central lines were inserted, and fluid resuscitation was guided by central venous pressure and clinical response. Norepinephrine was commenced at a rate of 120 µg/h, and she received 3.5 l of intravenous crystalloid in the first 4 h. Sodium bicarbonate was administered as 2×100 mmol boluses over 2 h and a further 200 mmol over the following 10 h, aiming for a pH of 7.45. No immediate effect was observed, but the QTc interval gradually decreased, returning to normal within 12 h. The patient was discharged after a 36 h period of observation.

DISCUSSION

The antiemetic effect of dolasetron is due to the antagonism of 5-hydroxytryptamine 3 receptors in the chemoreceptor trigger zone of the area postrema (Company datasheet). Dolasetron is well absorbed and rapidly converted to its active metabolite, hydrodolasetron, reaching maximum plasma concentration in 1 h. The absolute bioavailability is approximately 75%, and it is widely distributed, with an apparent volume of distribution of

Figure 1 ECG showing first-degree heart block, non-specific intraventricular conduction delay (IVCD) and prolonged QTc interval with repolarisation changes.

Table 1 Initial laboratory results including urinary drug screen

Parameter	Level	Normal range
Sodium (mmol/l)	138	135–145
Potassium (mmol/l)	4.2	3.6–5.1
Chloride (mmol/l)	104	95–107
Urea (mmol/l)	2.1	2.9–7.1
Creatinine (mmol/l)	78	60–110
Glucose (mmol/l)	6.7	3.0–5.5
Calcium (mmol/l)	2.09	2.25–2.58
Magnesium (mmol/l)	0.79	0.74–1.03
Haemoglobin (g/l)	107	115–165
White cells ($10^9/l$)	10.5	4.0–11.0
pH	7.32	7.32–7.42
PvCO ₂ (mm Hg)	49.5	41–51
PvO ₂ (mm Hg)	20.1	25–40
HCO ₃ (mmol/l)	25.2	22–31
Base excess	0.0	–2–2
Lactate (mmol/l)	1.9	<2
Paracetamol	negative	
Amphetamine	UDS-positive	
Opiate/cocaine/cannabinoids	UDS-negative	

PvCO₂, venous carbon dioxide tension; PvO₂, venous oxygen tension; UDS, urinary drug screen.

5.0–7.9 l/kg. Elimination is by renal excretion (30%) and hepatic metabolism, with a half-life of 8.1 h (Company datasheet). Dolasetron is well tolerated, with the most frequent adverse effects being headache, dizziness, tiredness, abdominal pain and constipation (Company datasheet). Intravenous doses of 5 mg/kg in healthy human volunteers do not produce changes in pupil size, mood or electroencephalogram tracings (Company datasheet).

Dolasetron blocks cardiac sodium channels, and ECG changes, including prolongation of PR, QTc and QRS intervals, have been reported.² An intravenous dose of 1000 mg in a 59-year-old man resulted in hypotension

lasting for 3 h, requiring 500 ml of plasma expander, dopamine and atropine (Company datasheet). ECG showed sinus rhythm and prolongation of PR, QRS and QTc intervals. Doses of 5 mg/kg intravenously or 400 mg orally have been safely given to humans.

Dolasetron is rapidly absorbed from the gastrointestinal tract, but charcoal may limit absorption if given within 1 h of ingestion. No antidote exists and it is not known whether dolasetron is removed by extracorporeal techniques, but it is unlikely given its large volume of distribution. Hypotension should be managed with intravenous fluid resuscitation, correction of underlying hypoxia or metabolic abnormalities,

and cautious use of vasopressors such as norepinephrine. Although hypocalcaemia is recognised as a cause of QTc prolongation, there is little doubt that the observed features were due to dolasetron toxicity, as the calcium remained low at 1.95 mmol/l after ECG had returned to normal. Unfortunately, a serum hydrodolasetron level was not measured but should be requested in all such cases.

Sodium channel block contributes to cardiotoxicity in dolasetron and tricyclic antidepressant overdose. Sodium bicarbonate is useful in reversing sodium channel block in tricyclic antidepressant overdose, and was used in an attempt to overcome sodium channel block, although we noticed no apparent benefit. Hypertonic saline has also been reported to be efficacious in reversing QRS duration and hypotension in tricyclic antidepressant overdose, but there are no trials demonstrating a beneficial effect of either agent in dolasetron overdose.³

CONCLUSION

Although reports suggest that dolasetron is safe in therapeutic doses and may simply cause transient and asymptomatic ECG changes, this case demonstrates that overdosage can lead to significant haemodynamic instability. As dolasetron becomes more commonly prescribed, doctors and patients need to be aware of the dangers associated with dolasetron in toxic doses.

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Figure 2 ECG showing normal PR, QRS and QTc intervals in the 21-year-old patient 12 h after treatment.

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REFERENCES

- 1 **Bazett HC**. An analysis of the time relations of electrocardiogram. *Heart* 1970;**7**: 353-70.
- 2 **Kuryshv YA**, Brown AM, Wang L, *et al*. Interactions of the 5-hydroxytryptamine 3 antagonist class of antiemetic drugs with human cardiac ion channels. *J Pharmacol Exp Ther* 2000;**295**:614-20.
- 3 **McCabe JL**. Experimental tricyclic antidepressant toxicity: a randomized, controlled comparison of hypertonic saline solution, sodium bicarbonate, and hyperventilation. *Ann Emerg Med* 1998;**32**(Pt 1):329-33.

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