Severe Hypertension and Bradycardia Secondary to Midodrine Overdose

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Abstract The objective of this case is to describe the pharmacokinetics and toxicity of midodrine in overdose. A 20 year old female ingested up to 350 mg midodrine while recovering in hospital from another overdose. She developed vomiting and severe hypertension (blood pressure [BP], 210/100 mmHg). Remarkable findings included a heart rate with a range of 43–60 beats/min, spontaneous respirations (20 breaths/min), and oxygen saturations of >95 % on FiO₂ 25 %, and a GS of 8. She was admitted to intensive care and had a normal non-contrast CT brain. She was treated with a glyceryl trinitrate patch (5 mg) and observed for 36 h with subsequent BP reduction to 124/81 mmHg and improved in conscious state. Midodrine and desglymidodrine concentrations were measured with liquid chromatography tandem mass spectrometry and were detected with 2-h post-ingestion at concentrations of 158.4 and 169.7 ng/mL, respectively. The parent drug concentrations rapidly decreased with an elimination of half-life of 1.6 h, and the metabolite initially increased and then decreased. The peak in blood pressure appeared to coincide with peak metabolite concentrations. Midodrine in overdose can potentially cause severe hypertension and reflex

bradycardia but given its short half-life treatment with vasodilator agents and supportive care is sufficient.

Keywords Vasopressor · Antihypotensive · Poisoning · Orthostatic hypotension

Introduction

Midodrine is a peripherally acting alpha-1-agonist used to treat conditions such as orthostatic hypotension [1]. We present a case of a young female who overdosed with midodrine and confirmatory corresponding drug concentrations during her clinical course.

Case Report

A 22 year old female was transported to a hospital via ambulance after a collapse at a night club. Her past history included post traumatic stress disorder, borderline personality disorder, and neurocardiogenic syncope. Her medications were midodrine 10 mg three times daily, fluoxetine 20 mg daily, and quetiapine 150 mg at night.

She arrived with a Glasgow Coma Scale (GCS) of 4, heart rate (HR) of 70 beats/min, and systolic blood pressure (BP) of 85 to 95 mmHg. An electrocardiogram (ECG) showed sinus rhythm, her renal function was normal, and paracetamol and salicylate were not detected. She was intubated for airway protection and admitted to the intensive care unit (ICU). She was extubated within 24 h and discharged to the ward with the following vital signs: BP 118/78 mmHg and HR 80 beats/min. She admitted to taking an unknown quantity of diazepam and alcohol preceding the collapse.

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Her vital signs on the ward 3 h prior to the following event were BP 106/65 mmHg and HR 80 beats/min with GCS 15. While on the ward, she had an episode of vomiting with subsequent reduction in conscious state. An urgent review identified up to seventy 5-mg tablets missing from her midodrine supply that had been brought in by her mother that day. She subsequently developed severe hypertension (BP, 210/100 mmHg). The time of ingestion was approximately 2.5 h prior to this based on retrospective history and her having access to the midodrine. Her immediate findings included a HR of 43 to 60 beats/min; spontaneous respirations 20 breaths/min; oxygen saturations greater than 95 % on FiO₂, 25 %; and GCS 8 comprising of general movement but not obeying commands and yawning but not responsive to pain stimuli.

She was readmitted to the ICU for observation, with no additional respiratory or hemodynamic support required. A non-contrast computer tomography brain did not reveal any intracranial pathology. A chest X-ray showed right lower zone opacity representing aspiration pneumonia. A nasogastric tube was placed due to vomiting, which was attributed to gastrointestinal side effects of the large midodrine dose. She was treated with a glyceryl trinitrate patch (5 mg) for 5 h and observed for 36 h, with subsequent BP reduction to 124/81 mmHg and improvement in conscious state and resolution of vomiting (Fig. 1).

She was transferred to the psychiatric ward where the patient confirmed ingestion of 350 mg of midodrine which was

supplied by her mother earlier that evening. She was discharged to community mental health follow up on day 3. Informed consent was obtained to publish this case report.

Four serum samples were available, one before and three after ingestion, and midodrine and desglymidodrine concentrations were measured with liquid chromatography tandem mass spectrometry (see appendix). Neither the parent drug nor the metabolite was detected 14 h prior to ingestion, and 2 h post-ingestion concentrations were 158.4 and 169.7 ng/mL for parent and metabolite, respectively (Fig. 1). The parent drug concentrations rapidly decreased with an elimination half-life of 1.6 h and the metabolite initially increased and then decreased. The peak effect on the blood pressure appears to coincide with the peak of the metabolite desglymidodrine concentration (Fig. 1).

Discussion

Midodrine is a potent peripherally acting alpha-1-agonist used in the treatment of orthostatic hypotension, recurrent reflex syncope and dialysis-associated hypotension [1–3]. Its mechanism of action is to increase peripheral venous resistance and decrease venous capacity, hence increasing the supine and standing blood pressure [4, 7]. Notable side effects include compensatory reflex bradycardia [5], urinary urgency or

Fig. 1 Plot of the measured midodrine (parent) and desglymidodrine (metabolite) concentrations (ng/mL) versus time (hr) (a). Plot of blood pressure (systolic [*inverted triangles*], diastolic [*triangles*]) and heart rate (*dashed line*) versus time (b)

retention, pilomotor reactions [2], pruritus and supine hypertension [1] and risk of bradycardia due to an alpha mediated vagal reflex [3]. Previous studies at therapeutic doses (10 mg) showed minimal or no central nervous system (CNS) side effects as it has poor absorption across the blood-brain barrier [5, 6].

Midodrine is well absorbed via the gastrointestinal route (oral bioavailability, 93 %) and rapidly metabolized to an active metabolite desglymidodrine systemically [3, 4]. Early studies measured desglymidodrine peak plasma concentrations in 60 to 90 min ranging from 25 to 56 ng/ml with a mean volume of distribution of 4 L/kg [5]. The elimination half-life of midodrine itself is 30 min whereas desglymidodrine is 3 h. Midodrine is cleared from plasma in 2 h; desglymidodrine can still be detected after 10 h [7]. A 10 mg midodrine dose lasts 4 h and corresponds to blood concentrations of desglymidodrine in excess of 15 ng/ml [8]. Our patient had concentrations at least 10-fold these concentrations with a slightly increased elimination half-life of the parent drug.

A case series on midodrine overdose was published as an abstract by the Swiss Toxicological Information Centre [9]. Six adults ingested midodrine in overdose with dose ranges between 50 and 130 mg. All experienced bradycardia without hemodynamic compromise: HR 35 to 47 bpm, systolic BP 140 to 183 mmHg. There was no mention of severe hypertension or treatment. A detailed case report of a 10-year old boy on midodrine 10 mg daily for orthostatic hypotension noted severe supine hypertension (systolic BP 150 to 220 mmHg, diastolic BP 100 to 130 mmHg) lasting for 19 days post cessation of midodrine [10]. We are unaware of any previous published case reports looking at serum midodrine concentrations in overdose or resulting in a hypertensive crisis. Our patient improved with supportive care and glyceryl trinitrate patch treatment.

The exact etiology of our patient's decreased conscious state remains unclear, but we hypothesize that it may be a result of the midodrine overdose. Blood-brain barrier permeability and CNS effects are unknown at excessively high blood concentrations, multiple times that of the original study by Zachariah et al. [5]. The same study also lists drowsiness as an adverse effect. However, there has only been one case noted of central nervous system depression by the midodrine manufacturer product information, with no other details mentioned [9]. Another possibility is that our patient developed an acute hypertensive encephalopathy, but other features of hypertensive encephalopathy including headache [11] could not be confirmed in our patient due to her altered conscious state. This is less likely as hypertensive encephalopathy typically starts 12 h after a sustained blood pressure increase, whereas our patient had only been hypertensive for a few hours. Co-ingestants were excluded in retrospect as our patient was in an acute medical ward and only had access to midodrine.

This case suggests that midodrine can potentially cause severe hypertension and bradycardia when taken in overdose. Effects on the CNS at such high doses remain unclear but drowsiness is a possible adverse effect. Given its relatively short half-life, vasodilator agents and supportive care are likely all that is required for treatment [9]. The peak hypertensive effects appeared to peak with the metabolite concentrations.

Compliance with Ethical Standards Informed consent was obtained to publish this case report.

Conflicts of Interest The authors declare that they have no conflicts of interest.

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Informed Consent Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

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