CASE REPORT

Pramipexole Overdose Associated with Visual Hallucinations, Agitation and Myoclonus

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Abstract

Introduction Pramipexole is a dopamine D₂ receptor agonist used to treat idiopathic Parkinson's disease and primary restless legs syndrome. There is limited information on pramipexole overdose.

Case Report A 59-year-old male ingested 3 mg pramipexole, 2250 mg venlafaxine, 360 mg mirtazapine, with suicidal intent. He presented alert, had normal vital observations and normal pupillary reflexes. He was mildly agitated, reported visual hallucinations and was given 5 mg diazepam. He had a mildly elevated lactate of 1.7 mmol/L, but otherwise normal laboratory investigations. Overnight, he remained agitated with visual hallucinations and developed myoclonus while awake. He had increasing difficulty passing urine on a background of mild chronic urinary retention. On review, 14 h post-ingestion, he was hypervigilant, jittery and mildly agitated. He had pressured speech and difficulty focusing on questioning. He had a heart rate of 110 bpm, but had an otherwise normal examination,

with no clonus or extrapyramidal effects. He was unable to mobilize due to dizziness and ataxia. Over the next few hours, he improved, the visual hallucinations and agitation resolved and he mobilized independently. Pramipexole was measured with liquid chromatography mass spectrometry. The initial plasma pramipexole concentration was 34.2 ng/mL (therapeutic range 0.2 to 7 ng/mL), 9 h post-overdose. Concentration time data fitted a one-compartment model with an estimated elimination half-life of 18 h.

Discussion Pramipexole overdose with hallucination, agitation, and myoclonus is consistent with adverse effects reported with therapeutic toxicity, but mirtazapine and venlafaxine may have contributed. Pramipexole concentrations exceeded the therapeutic range for over 24 h. With the increasing use of pramipexole in restless legs syndrome, adult overdoses may become more common.

Keywords Pramipexole · Overdose · Toxicity · Hallucinations · Agitation

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Introduction

Pramipexole is a non-ergot-derivative dopamine D₂ receptor agonist [1] and is used to treat idiopathic Parkinson's disease and primary restless legs syndrome [2, 3]. Deliberate self-poisoning from ingestion of pramipexole is rare and there are few case reports. Reported side-effects in patients taking pramipexole in therapeutic doses include somnolence, dizziness, nausea and vomiting, headache, insomnia, extrapyramidal effects, hallucinations and behavioural changes [4–6]. We report an overdose of pramipexole with venlafaxine and mirtazapine causing agitation and hallucinations.

Case Details

A 59-year-old male was brought to the hospital 5 h after ingesting 3 mg pramipexole, 2250 mg slow-release venlafaxine, 360 mg mirtazapine, with suicidal intent. The pramipexole was prescribed for restless leg syndrome—0.125 mg daily. He took venlafaxine 150 mg once daily, mirtazapine 15 mg once daily and was also on fludrocortisone for postural hypotension. In the emergency department, his vital signs were Glasgow Coma Scale (GCS) 15, respiratory rate 18/min, oxygen saturation 97% on room air, heart rate (HR) 85 bpm and blood pressure (BP) 125/75 mmHg. He had normal pupillary sizes and reflexes. He was mildly agitated and reported visual hallucinations. He was given 5 mg diazepam for the agitation and was admitted to the emergency short stay unit for observation and intravenous fluids. He did not receive any decontamination. He developed a sinus tachycardia on his electrocardiogram with a HR of 102 bpm. Initial laboratory investigations were blood glucose concentration 7.8 mmol/L (reference range (RR) 3.9–5.8 mmol/L), lactate 1.7 mmol/L (RR 0.5–1.6 mmol/L) and pH 7.37 (RR 7.32–7.43). He had normal full blood count, creatinine and electrolytes.

Overnight, he continued to report visual hallucinations (spiders crawling in the room, an unknown man sitting on the chair next to his bed). He had never previously experienced hallucinations. He remained agitated overnight and developed myoclonus. He described the myoclonus as being so strong he was afraid he would fall out of bed. There was no other evidence of severe serotonin toxicity on neurological examination, with a normal temperature, no ankle or ocular clonus, no tremor or increased tone. He did not meet the Hunter Serotonin Toxicity Criteria [7]. He had increasing difficulty passing urine on the background of mild chronic urinary retention, with post-void residual volume of 250 mL, but did not require an indwelling catheter. His urinary retention resolved on the following day and a post-void bladder scan did not show any residual urine volume.

When reviewed by the toxicology team 14 h post-ingestion, he appeared hypervigilant, jittery and mildly agitated. He had pressured speech and difficulty focusing on questioning. He was tachycardic with a HR of 110 bpm, and his other observations were otherwise unremarkable. He did not have a tremor or any evidence of dystonia or extrapyramidal effects. He was unable to mobilize due to postural dizziness and unsteadiness, but did not have postural hypotension. His reflexes were brisk but there was no increased tone or ankle clonus. Over the next few hours, his symptoms improved and he no longer experienced visual hallucinations or agitation and was able to mobilize independently. He was medically cleared and transferred to a mental health facility.

Blood was collected for subsequent analysis, centrifuged, plasma separated and frozen (see [appendix](#)). A validated liquid chromatography mass spectrometry assay was developed to measure the pramipexole concentrations in plasma [8–10]. The

initial plasma pramipexole concentration was 34.2 ng/mL (therapeutic range 0.2 to 7 ng/mL [11]) approximately 9 h post-overdose. The pramipexole concentration then decreased to 13.4 ng/mL at 25 h, 15.0 ng/mL at 36 h and 8.5 ng/mL at 47 h. The concentration time data were fitted to a one-compartment model with an estimated elimination half-life of 18 h (Fig. 1). Written consent for publication of this case was obtained and provided to the journal.

Discussion

We report an adult patient ingesting an overdose of pramipexole with venlafaxine and mirtazapine who suffered visual hallucinations, confusion and agitation requiring admission for 24 h and oral sedation. He also suffered myoclonus, ataxia and worsening of his underlying urinary retention. These effects were consistent with previous reports of pramipexole toxicity [12, 13]. Although he co-ingested 2250 mg of venlafaxine and 360 mg of mirtazapine, neither of these drugs has been reported to cause this particular combination of clinical effects, based on large case series of overdoses [14–16].

There is little published information on acute overdose of pramipexole, with no previous published cases in adults and limited information in children [17]. Hang et al. report an ingestion of 1 mg pramipexole in a 17-month-old child who developed lethargy and had early vomiting, but no other neurological effects. They refer to unpublished cases reported by the manufacturer in 11 children which caused sedation, ataxia, vomiting, rashes and tachycardia. One case in an adult ingesting 11 mg/day for 2 days caused tachycardia [17].

Our case is more consistent with previous reports of toxicity or less common adverse effects with therapeutic use, wherein the major features of toxicity are hallucinations, agitation, psychosis and extrapyramidal effects [5, 12, 13]. For

Fig. 1 Logarithmic linear plot of pramipexole plasma concentrations (ng/mL) versus time post-overdose with an estimated half-life of 18 h

example, hallucinations appear to be dose-related, being more common in patients treated with larger doses (1.5–4.5 mg daily) of pramipexole for Parkinson's disease, compared to smaller doses (0.125–0.75 mg before sleep) in restless legs syndrome [6, 18]. Although these neuropsychiatric manifestations may not be life-threatening, they are difficult to manage and usually require sedation and longer lengths of stay. Larger overdoses may also be associated with more significant complications, such as seizures and coma.

Pramipexole is rapidly absorbed in therapeutic doses with peak concentrations within 2 h of ingestion. It has a bioavailability greater than 90% and the majority is excreted renally with minimal hepatic metabolism [19, 20]. The elimination half-life in our patient was 18 h, so slightly longer than the reported half-life of 8 to 14 h in therapeutic use [11]. The plasma concentrations were also above the reported therapeutic range of 0.2 to 7 ng/mL for over 24 h [11].

It is difficult to definitely attribute all of the symptoms in this case to pramipexole alone due to the co-ingestion of venlafaxine and mirtazapine. However, the vivid hallucinations and confusion in addition to agitation are rarely seen with either venlafaxine or mirtazapine overdose. Mirtazapine principally causes drowsiness in overdose [14], but has been reported to cause agitation and non-specific neuromuscular excitation with therapeutic use. Venlafaxine has been reported to cause myoclonus as part of serotonin toxicity in overdose [16], but the patient had few other features of serotonin toxicity and did not meet the criteria for serotonin toxicity, with no clonus, hypertonia or tremor [7]. There are reports of isolated visual hallucinations and myoclonus with therapeutic venlafaxine and mirtazapine [21–23], but not in overdose. In contrast, hallucinations are a common side-effect of large therapeutic doses of pramipexole in treatment for Parkinson's disease, with 17% of patients reporting it and it being the commonest reason for stopping the drug [6]. Interestingly, both mirtazapine and venlafaxine have been reported to cause restless legs syndrome [24, 25], so our patient may not have had primary restless legs syndrome.

A potential limitation of the report is that mirtazapine and venlafaxine were not confirmed analytically. However, including the concentrations of these drugs only confirms that they were taken and not that they were the reason for the effects seen in the patient.

Our patient experienced visual hallucinations, confusion, agitation and myoclonus within a few hours of the pramipexole overdose with co-ingestion of venlafaxine and mirtazapine. Both the myoclonus and the visual hallucinations had resolved within 15 h post-ingestion with supportive care. Pramipexole was most likely the drug responsible for the symptoms seen in our patient although both venlafaxine and mirtazapine may have contributed to the movement disorder and agitation. With the increasing use of pramipexole in restless legs syndrome, adult overdoses may become more

common and further reports are required to confirm the features of pramipexole overdose.

Compliance with Ethical Standards

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

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Conflict of Interest The authors declare that they have no conflict of interest.

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