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CASE REPORT

A rare case of auto-intoxication with an antidote: fampridine

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Abstract

A 57-year-old female was admitted to the intensive care unit (ICU) after an attempted suicide with fampridine. She was comatose and experienced multiple seizures. Moreover, during her ICU stay she developed rhabdomyolysis and acute kidney injury. To our knowledge, this is one of the few case reports on attempted suicide by an auto-intoxication with fampridine.

Introduction

In this case report we present a rare case of attempted suicide: an auto-intoxication with fampridine. This potassium channel blocker improves walking in patients with multiple sclerosis and is used as an antidote to treat intoxications with calcium channel blockers. Only a few case reports have described intoxications with fampridine, mostly accidental and unintentional. However, according to the literature, cases concerning intentional fampridine overdoses in the context of attempted suicide are scarce.

Case report

A 57-year-old female presented to the emergency department with an altered mental status. She was found comatose in her own residence. Empty medication strips indicated a possible intoxication with 600 mg of fampridine (60 tablets of 10 mg). This potassium channel blocker was prescribed in 2016 to reduce walking difficulties associated with multiple sclerosis (relapsing remitting type), diagnosed in 1990. Further medical history revealed multiple attempted suicides, depression and histrionic personality disorder. Recently, she had received a new batch of fampridine, a supply for at least three months. Besides fampridine, she was not receiving any other medications.

On admission to the emergency department, she was comatose with a Glasgow Coma Scale score of three and had multiple convulsions for which she was sedated, intubated, and admitted to the intensive care unit (ICU). The convulsions were treated with propofol. Because of the ingestion of slow-release tablets, we treated her with repeated oral administration of activated charcoal for the first two days. On physical examination she had normal pulmonary sounds and an oxygen saturation of 96% on mechanical ventilation on a FiO_2 of 21%. She was haemodynamically stable (blood pressure 105/55 mmHg, heart rate 81 beats per minute). Neurological examination showed nystagmus with conjugate eye deviation to the right side. Her pupils were equal and reactive to light. There was no nuchal rigidity and the glucose level was normal. Besides, neither fever nor hypothermia were objectified. An additional electrocardiogram showed no abnormalities, aside from a slightly prolonged corrected QT time of 485 ms. Structural intracerebral causes of convulsions and coma were excluded through a CT scan. Lastly, paracetamol levels in blood serum were tested and found undetectable. The patient spent the night in the ICU after which the propofol was discontinued the next morning. Five hours after cessation, the patient remained unconscious (E1M3Vtube). However, nystagmus and convulsions were no longer observed. The corneal reflex was present. After gradually regaining consciousness during the next day (second day after cessation of propofol), the ventilator support could be stopped and the patient was extubated. The ICU stay was complicated by hypertension for which administration of labetalol and captopril was necessary. Furthermore, a suspected aspiration pneumonia was treated with amoxicillin/clavulanic acid. Slowly recovering acute kidney injury (with highest creatinine level of 249 µmol/l), possibly due to rhabdomyolysis (with highest creatine kinase level of 14,399 U/l) was treated with hyperhydration. She was discharged to the psychiatric ward after six days in the ICU. On psychiatric evaluation, the attempted suicide seemed to be an impulsive action based on progression of multiple sclerosis, a feeling of helplessness and difficulties in paying the rent. After

a nine day stay on the psychiatric ward and therapy sessions, she was free of active suicidal thoughts and could be discharged home where psychological follow-up took place.

Discussion

4-aminopyridine is a nonspecific potassium channel blocker that was developed in 1963 by Philips Petroleum Co. as a bird repellent named Avitrol.[1] By blocking potassium channels, calcium influx is stimulated and acetylcholine is released in the synapse. Consequently, action potentials are prolonged, repolarisation is delayed, and neuromuscular transmission is enhanced. Patients suffering from multiple sclerosis or spinal cord injury might benefit in terms of ambulatory improvement. Various studies have shown verbal fluency improvement and gait enhancement of at least 35% in multiple sclerosis patients on fampridine therapy.[2,3] Since fampridine crosses the blood brain barrier and tends to restore conduction in demyelinated axons, a reduction of spasticity and thereby an improvement in functionality has also been documented in patients suffering from spinal cord injury.[4] Although 4-aminopyridine was introduced in the early 1960s, it was not until 2010 when the Food and Drug Administration (FDA) approved its use in humans. Intoxications with fampridine have been occurring sporadically, both before and after the FDA's approval.[5-8] Most case reports describe accidental intoxications in multiple sclerosis patients on fampridine therapy.[5,6,9,10] The majority of these accidental intoxications are caused by pharmacy compounding errors, self-medication, and medication mix-ups.[5,6,9-13] Only a few case reports concerning intentional overdoses with fampridine have been published.[7,8,10] Although one patient was known with social stress and insomnia leading up to the auto-intoxication,[8] a history of depression was not described in any of the cases.

According to the current literature, the clinical picture of fampridine intoxication can vary from diaphoresis and agitation to status epilepticus.[9] Tremors and choreatic movements cover the centre of the spectrum.[10] Aside from neurological symptoms, a fampridine intoxication can lead to supraventricular tachycardia[13] and hypertension,[6] similar to our case. The seizure risk when taking the standard dose (10 mg every 12 hours) of fampridine is stated not to be higher than the baseline risk of seizures in patients with multiple sclerosis, which is roughly four times higher than in the general population.[14] However, the incidence of adverse events, especially of seizures, appears to be dose related.[15] Studies that show an elevated risk of seizures reported higher doses of fampridine,[15], renal impairment,[16] concurrent use of other (epileptogenic) medication and subcortical lesions.[17]

Treatment of fampridine overdose consists primarily of symptom control and reduction of fampridine absorption.[7,8,11,12] Symptoms are managed by intubation, mechanical ventilation and burst suppression of convulsions by use of intravenous sedatives or antiepileptic drugs. A study in mice by Yamaguchi et al. showed that phenytoin-like drugs were protective for fampridine-induced seizures, whereas benzodiazepines and GABA enhancers were less effective.[18] Yet, in current case reports, intravenous administration of propofol, lorazepam or diazepam are mentioned frequently.[5,7,10-12] To reduce absorption, administration of (repeated) activated charcoal, gastric lavage and whole bowel irrigation are part of regular intoxication practice. However, the window for these interventions in fampridine is relatively narrow: one to four hours, depending on the time to maximal plasma concentration of immediate-release and slow-release tablets, respectively.[19,20] Aside from this, our patient received hyperhydration to manage the rhabdomyolysis. This may have aided fampridine excretion, since the drug is primarily excreted via urine.[21]

Fampridine itself is used to treat calcium channel blocker (CCB) overdoses.[22] Intoxications with CCBs are the second most common cardiovascular drug poisonings. They are potentially lethal and therefore warrant ICU admission. Symptoms of CCB intoxication are bradycardia or other rhythm disturbances, as well as hypotension (due to vasodilation and reduction of ventricular contraction).[23]

Verapamil poisoned rats receiving fampridine showed a higher survival rate and a faster shock reversal (within 10 minutes of administration) compared with calcium, adrenaline and levosimendan.[24,25] These results are supported by a few case reports indicating shock reversal in CCB intoxicated patients treated with fampridine.[22]

Currently, there is no guidance on fampridine dosing in CCB intoxications. Rat models show fasciculations in all rats receiving 2 mg/kg/h continued infusion,[25] whereas lowering the dosage to a continued infusion of 1 mg/kg/h resulted in loss of the ability to reverse shock.[26] In a case report by Wilffert et al., amlodipine poisoning was treated with 50 µg/kg/h of fampridine over three hours, causing an immediate rise of blood pressure without side effects.[22] This lack of knowledge on and evidence for the correct dosing could then again lead to fampridine intoxications in ICU patients treated for CCB poisoning, emphasising the importance of understanding the clinical picture and treatment.

Conclusion

This case report describes the potential risks of intentional auto-intoxication with fampridine. Patients are at risk of a variety of complications that could require admission to the ICU. As shown by our case, treatment of symptoms and absorption reduction of fampridine are crucial. On presentation of a known multiple sclerosis patient with an altered consciousness and

seizures, fampridine overdose should be considered. However, intensivists in particular should be aware of the toxic effects of this potassium channel blocker in patients treated for CCB overdose as well.

Disclosures

All authors have no conflicts of interest to declare. No funding or financial support was received. The institutional review board waived the need for informed consent.

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