Intravenous lipid emulsion for a life-threatening prothipendyl intoxication

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SUMMARY

Prothipendyl, a lipophilic neuroleptic drug, requires a careful dosage regimen due to its potential side effects, including life-threatening arrhythmias. This report outlines a case of severe prothipendyl intoxication, its management and the successful utilisation of Intralipid, an intravenous lipid emulsion, in treating ventricular arrhythmia postmassive prothipendyl ingestion. Additionally, the mechanism of action of Intralipid and the rebound concentration of the lipophilic drug in such scenarios are discussed.

BACKGROUND

Prothipendyl, a tricyclic azaphenothiazine neuroleptic drug with weak antipsychotic effects, is primarily prescribed for agitation, sleep disorders and anxiety. Its administration requires meticulous attention due to its potential to prolong the QT interval, predisposing patients to life-threatening arrhythmias.[1]

In this paper, we discuss a case of prothipendyl intoxication managed in our intensive care unit (ICU).

CASE PRESENTATION

A 30-year-old woman, with a history of bipolar disorder, sleep disorder and anxiety, was admitted to the emergency department (ED) following intentional ingestion of 50 tablets of prothipendyl 50 mg, 10 tablets of zolpidem 10 mg and 40 tablets of lorazepam 2.5 mg. She is of normal build (body mass index 23.7 kg/m^2) and has no allergies.

On presentation, she was drowsy with an otherwise unremarkable clinical examination. Her ECG revealed a prolonged QT interval (770 ms). She was initiated on magnesium sulfate in the ED and subsequently transferred to the ICU for advanced monitoring. Shortly postadmission, she developed haemodynamic instability, presented with torsade de pointe followed by ventricular fibrillation, necessitating external electrical defibrillation. She was intubated and placed on mechanical ventilation. Despite initial successful intervention, recurrent life-threatening ventricular arrhythmias recurred. Consequently, 20 hours postingestion, we initiated Intralipid 20% infusion. Following a bolus of 1.5 mL/kg over 1 min, a continuous infusion of 0.25 mL/kg/min was started and then ceased 12 hours later due to the resolution of arrhythmias, even with a persistently increased QT interval (550 ms). There was no recurrence of arrythmia thereafter. The patient later developed ventilator-associated pneumonia, which was managed with amoxiclav for 5 days. She was extubated successfully on day 3 of her ICU stay.

OUTCOME AND FOLLOW-UP

The patient was discharged from the ICU on day 6 in stable condition. Serial measurements of prothipendyl and benzodiazepine serum concentrations are illustrated in figure 1.

DISCUSSION

This case highlights the dangerous cardiac arrhythmias that may occur postprothipendyl overdose, and the therapeutic efficacy of intravenous lipid emulsion (ILE) (Intralipid). Data on severe prothipendyl intoxication are limited. Doses exceeding 4 g have been reported to be lethal (our patient took 2.5 g), and serum concentrations surpassing 200 times the therapeutic range (66 times in our case) have been described as particularly toxic.[2]

Prothipendyl is a lipophilic neuroleptic drug commonly prescribed to treat psychological disorders. It can induce severe arrhythmia by increasing QT interval, underscoring the need for careful monitoring.[1 3] The recommended therapeutic range is 5–20 ng/mL (for sleeping disorder) and 30–80 ng/mL (for acute sedation). The laboratory alert level is 500 ng/mL.[4] The serum concentration of prothipendyl may fluctuate due to factors such as drug-to-drug interactions, delayed absorption and metabolism, prolonged absorption, accumulation, and delayed release of the active compound.[5] Only few pharmacokinetic data are available in the literature. Considering their molecular similarity, in the absence of specific data, it has been suggested to use the characteristics of perphenazine to describe the pharmacokinetic properties of prothiendyl.[6] The half-life of this drug ranges from 2 to 20 hours.[7] Metabolism of prothipendyl is mainly mediated by CYP enzymes (CYP1A2, CYP2D6, CYP2C19 and CYP3A4). Isoforms CYP2C19 and CYP1A2 are predominantly implicated in the formation of N-demethyl-prothipendyl. The CYP isoenzyme 3A4 is responsible for the formation of prothipendyl sulfoxide.[1] Peak plasma concentration is reached 2–4 hours after oral intake. Tissue distribution is important with a volume of distribution of 3 L/kg. Because of its high lipophilicity, prothipendyl accumulation in the brain, lungs

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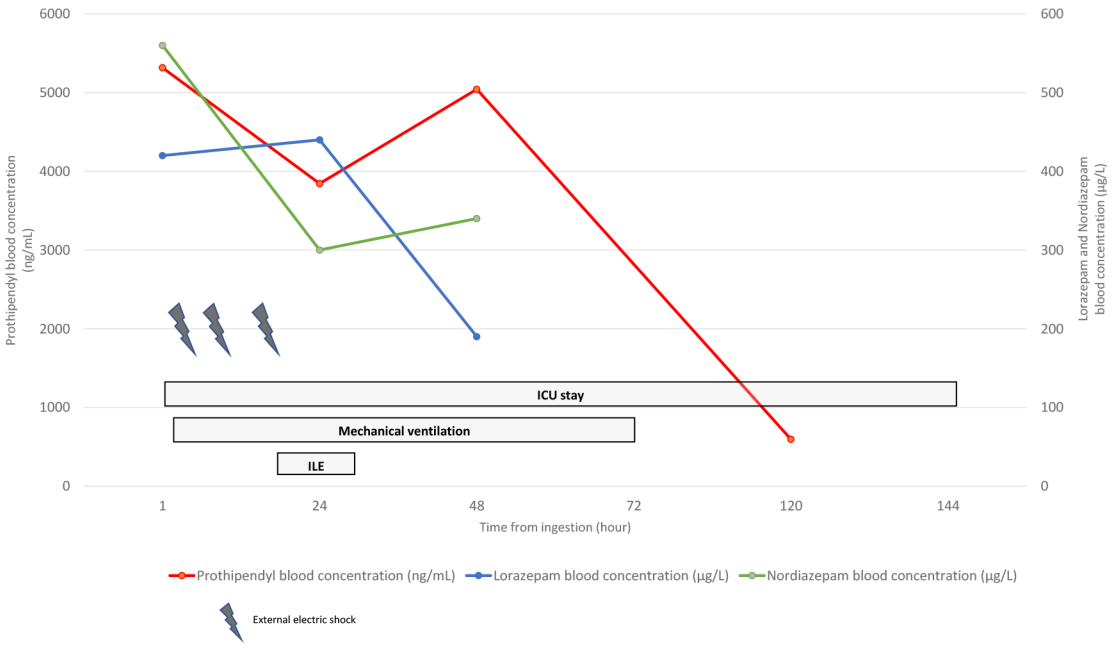

Figure 1 Plasmatic drugs concentration and clinical events. ICU, intensive care unit; ILE, intravenous lipid emulsion.

and other highly vascularised tissues is significant. The products of the hepatic metabolisation are excreted via the kidneys and enterohepatic circulation.

ILE is a recognised treatment for lipophilic drug poisoning, although with limited supporting evidence.[8 9] The ILE binding mechanism depends on the lipid/water partition coefficient and on the distribution volume. The lipid/water partition coefficient is an indicator of drug lipophilicity: the higher the coefficient, the greater the lipophilicity of the drug (and its ability to cross the cell membrane). The lipid/water partition coefficient is appreciated with the logP. A drug is considered lipophilic if its logP is >1.72. The logP of prothipendyl is 3.4, while it is 2.5 and 2.4 for zolpidem and lorazepam, respectively. Such logPs indicate that these drugs are lipophilic.[10]

The mechanism of action of ILE in case of intoxication with a lipophilic drug remains elusive. However, the 'lipid sink' phenomenon, where lipophilic drugs are sequestered into the plasma liquid phase, thereby delaying their distribution and action on target tissues, is widely accepted.[8] For example, after lipid infusion, Heinonen *et al* showed that the concentration of amitriptyline decreased in brain tissue and, to a lesser extent, in cardiac tissue. In contrast, after the start of lipid infusion, the arterial plasma concentration of amitriptyline was rather stable or even increased temporarily. This observation suggests the ability of lipid-rich plasma to draw a lipophilic molecule.[11] ILE may also act via 'lipid shuttle', a mechanism according to which a lipid emulsion can absorb lipophilic molecules and transport them from highly perfused organs to the liver and muscles where detoxification and storage may occur.[12 13]

The current guidelines recommend that ILE is administered as an initial bolus of 1.5 mL/kg (lean body mass) over 1–2 min, followed by a continuous infusion at the rate of 15 mL/kg/hour. If the instability persists, two extra boluses of 1.5 mL/kg may be considered and the infusion rate may be increased up to 30 mL/kg/hour.[14] ILE might be considered in case of severe cardiovascular instability due to a lipophilic drug intoxication when conventional measures fail.[12 15 16]

In our patient, clinical deterioration and life-threatening arrhythmias manifested early posthospitalisation, prompting Intralipid initiation. The decision to administer ILE was based on clinical indicators rather than blood concentration iterative measurements, which are not routinely available. The observed increase in prothipendyl blood concentration 48 hours postintoxication, despite clinical amelioration, might be attributed to the drug's pharmacokinetic properties and the lipid sink and shuttle theory. It may also be explained by the competition between lorazepam, zolpidem, prothipendyl, three lipophilic drugs that may interact with ILE. Finally, a wide range of prothipendyl blood concentrations have been reported and explained by drug-to-drug interaction, absorption and metabolism competition, and redistribution (high volume of distribution).[5]

In summary, we report a case of intentional prothipendyl poisoning resulting in life-threatening ventricular arrhythmia, which was successfully managed with ILE infusion. While the evidence supporting ILE's use in lipophilic drug intoxication remains weak, it is recommended in patients with life-threatening conditions unresponsive to conventional treatments. Intensive and prolonged monitoring is crucial due to the potential for delayed rebound in lipophilic drug plasma concentrations.

Learning points

- Prothipendyl intoxication may be severe and life-threatening.
- Intensive and prolonged monitoring is crucial postlipophilic drug intoxication due to the potential for delayed rebound in plasma drug concentrations.
- While evidence supporting intravenous lipid emulsion in managing lipophilic drug overdose is scant, it is recommended in life-threatening situations where conventional treatments fail.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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