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CASE REPORT

Calypso's spell: accidental near-fatal thiacloprid intoxication

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Key Clinical Message

Acute life-threatening intoxications with insecticides are rare. We report a case of accidental near-fatal thiacloprid intoxication with mass spectrometry-based analytical confirmation. The initial clinical presentation resembled imminent brain death and/or severe postanoxic encephalopathy. Prolonged supportive treatment resulted in full recovery underlining intoxication as an important differential diagnosis in unclear coma.

Keywords

Hemodialysis, ICU, insecticide, intoxication, nicotinamide, thiacloprid.

Introduction

Neonicotinoids are widely used insecticides with several compounds being commercially available (imidacloprid, thiacloprid, acetamiprid) [1–3]. Neonicotinoids act as agonists on nicotinic acetylcholine receptors (nAChRs) inducing the disruption of neural transmission in the central nervous system via mimicking of neurotransmitter action and/or continuous nerve stimulation or blocking [1, 4–6]. Tissue penetration and translocation characteristics account for a relevant toxicity in insects resulting in paralysis, cellular exhaustion, and death [7]. Importantly, differences in nAChR subtypes/specificity of binding sites, reduced nAChR expression, and poor mammalian blood–brain barrier penetration account for an assumed low toxicity in vertebrates [4, 7–12]. Classification of thiacloprid toxicity is largely based on animal data with potential differences between specific products [12, 13].

Reports on acute life-threatening intoxications with neonicotinoids in humans are rarely observed on intensive care units and are mostly limited to acetamiprid and imidacloprid [14]. Few previous reports exist on fatalities following acute thiacloprid intoxication [15]. Here, we present a case of a near-fatal acute accidental thiacloprid intoxication. Subsequent complete recovery was observed after a prolonged course of extensive supportive intensive care treatment.

Case History

A 72 year-old previously healthy Caucasian male prepared coffee in a hunting cabin in the woods. From a nearby windowsill a "milk" bottle was grabbed and a substantial amount (around 100–200 mL) added to a "Café au Lait." Although the patient noticed the last "milk" drops got fluffy, he finished his "Café au Lait" in one go. About 15 min later, severe nausea and repeated vomiting was noted and emergency teams were called for by his fellow hunters. When paramedics arrived at the scene, an unconscious patient with lateralized convulsions was noted, and benzodiazepines administered. After cessation of convulsions, the patient was transported to a rural emergency

department with coma of unknown origin. Persisting coma subsequently required mechanical ventilation. Predominantly facial and thoracal myoclonia developed shortly thereafter, and hypothermia (core body temperature 31.8°C), progressive metabolic acidosis (pH 7.09, HCO_3^- 14 mmol/L) with increased serum lactate (6 mmol/L), hypokalemia (2.6 mmol/L), and hypocalcaemia (1.91 mmol/L) was noted. Repeated testing of serum glucose levels returned normal. Despite adequate fluid resuscitation, volume-refractory hemodynamic shock with need for high-dose noradrenaline was noted (0.7 mcg/kg/min). A cerebral contrast-enhanced CT scan returned normal.

Treatment at Tertiary Care Unit

The differential diagnosis of unclear persisting coma with acute-onset typically embraces cerebral vascular disorders/stroke, seizures, advanced cerebral or systemic infections, (traumatic) brain injury, hypo- (or hyper) glycemia, postanoxic/postcardiac arrest, organ failure-related (incl. endocrine disease), metabolic/electrolyte-induced, and importantly, intoxications (e.g., alcohols). After retrieval of the presumed "milk bottle" (thiacloprid concentration: 480 g/L), severe accidental acute thiacloprid intoxication appeared obvious and transfer to our tertiary care academic center was performed. At ICU admission, an intubated comatose patient with progressive metabolic acidosis (pH 6.9) and hyperdynamic volume-refractory vasoplegic shock was noted. As metabolic acidosis was unresponsive to sodium bicarbonate infusions, emergency hemodialysis was performed (Fig. 1A, blood flow 250 mL/min., dialysate flow 600 mL/min., bicarbonate dialysate, urea reduction rate approx. 44%, kt/V 0.91). The diagnosis was confirmed analytically with levels of thiacloprid and metabolites being followed up by mass spectrometry (Fig. 1). Supportive care was continued, and metabolic acidosis and hemodynamic shock gradually improved over the subsequent 12–24 h.

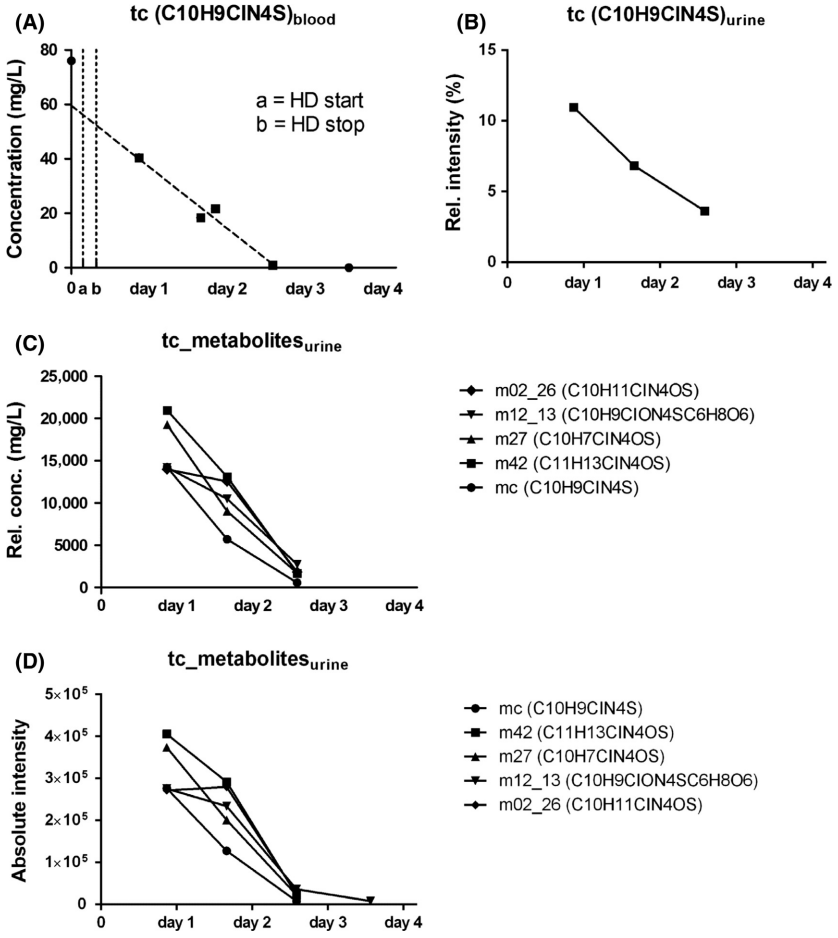

Figure 1. Evolution of thiacloprid and metabolite levels in plasma and urine. Course of plasma (A) and urinary (B–D) levels of thiacloprid or metabolites (LC-MS). (1A): Time of hemodialysis is given (a, b); dotted line: linear regression line day 1–3. (B) Course of relative intensity of the main compound in urine (%), (C) relative urinary concentrations of key metabolites, and (D) absolute urinary metabolite intensities are given.

Repeat neurological examination off sedatives revealed a comatose patient (GCS 3) with maximal dilated and fixed pupils, absent corneal and vestibulo-ocular reflexes without reaction to painful stimuli. Intermittent irregular multifocal facial and (mostly upper) extremity myoclonus with "hemiballistic-type" movements most likely due to disrupted neurotransmission and/or altered nerve conduction velocity were noted (Video S1). Electroencephalography showed alpha-theta waves without status epilepticus and only minimal variability and responsiveness to stimuli. Cerebral MRI demonstrated minor cortical diffusion restriction in the postcentral gyrus.

Outcome and Follow Up

On day 2 (serum levels <30 mg/L, Fig. 1A), neurologic improvement was noted with reversal of coma, spontaneous eye opening, obeying of simple commands, but persistence of extensive myoclonus. Over the ensuing days, steady neurological improvement was observed, and extubation was performed on day 4. On day 8, the patient had fully recovered and was discharged home.

Discussion

Human data on severe acute intoxications with thiacloprid are sparse [15]. Here, repeat analysis of the patient's plasma and urine levels for the main thiacloprid compound as well as key metabolites was performed using liquid chromatography mass spectrometry (LC-MS) (Fig. 1A–D). Serial assessment of toxin levels by LC-MS in plasma and urine revealed progressive and near-complete decrease in thiacloprid levels (blood: 76.05–0.011 mg/L) until ICU discharge at day 4 (Fig. 1A–D).

A decline in thiacloprid plasma concentrations was observed until day 3 (Fig. 1A, dotted line: linear regression day 1 to day 3). Unfortunately, neither blood samples drawn exactly before and after hemodialysis, nor dialysate samples were available for technical reasons and we can thus only speculate on whether toxin removal can be achieved by hemodialysis. However, in goats, hens, and rats, thiacloprid elimination was described to mainly occur via the renal route, with hydroxylation and glucuronidation being key initial metabolic steps (http://dissemination.echa.europa.eu/Biocides/ActiveSubstances/0053-08/Data_002.pdf. assessed 11 December 2016). Interestingly, a rather constant decline of thiacloprid blood levels was observed over the whole concentration range during the days following the dialysis procedure (Fig. 1A) which might theoretically hint to a zero order kinetic by an active saturable transport rather than "simple" free glomerular filtration. Extracorporeal elimination using hemodialysis might therefore be of benefit to overcome the limited renal elimination capacity especially during the initial phase with very high thiacloprid blood concentrations. To the best of our knowledge, however, a formal volume of distribution and plasma protein binding characteristics in humans are unknown and it should be kept in mind that plasma thiacloprid concentrations may not adequately reflect the degree of clinical severity [14]. Nevertheless, rescue hemodialysis might be considered in severely intoxicated patients for reasons beyond control of severe metabolic acidosis.

Conclusion

In conclusion, acute life-threatening thiacloprid intoxication is rarely observed in humans. The clinical presentation may masquerade as coma with clinical signs of imminent brain death and/or severe myoclonic status due to postanoxic encephalopathy. Despite an initial *at a first glance* futile clinical presentation, rare cases of severe intoxications must be considered when treating patients with persisting and unexplained coma. In cases with thiacloprid intoxications, prolonged supportive intensive care treatment seems indicated.

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Consent

Written informed consent was obtained from the patient for publication of this report.

Authorship

PZ, DG, NS, MN, and JCS: collected all data and drafted the manuscript. SK: performed expert laboratory toxicological investigations. JCS: coordinated the input of all authors. All authors read and approved the final version of the manuscript.

Conflict of Interest

The authors report no declarations of interest.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Video S1. Clinical presentation of intoxicated patient. Neurological presentation of the patient 24 h following ICU admission.

