Annals of Case Reports
Van Noort BB, et al. Ann Case Rep: 9: 102022
www.doi.org/10.29011/2574-7754.102022
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Case Report

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Treatment of Massive Paracetamol Overdose with Hemodialysis and Fomepizole; A Case Report

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Citation: Van Noort BB, van Eck van der Sluijs A, Benoist GE, Van Den Oever HLA (2024) Treatment of Massive Paracetamol Overdose with Hemodialysis and Fomepizole; A Case Report. Ann Case Report. 9: 2022. DOI:10.29011/2574-7754.102022

Received: 16 October 2024, **Accepted:** 21 October 2024, **Published:** 23 October 2024

Abstract

Paracetamol is often involved in (intentional) overdose, resulting in roughly 2,600 annual hospitalizations in the United States and being the second most common cause of liver transplantation worldwide. In massive overdose (ingestion of > 500 mg/kg), standard treatment protocol alone may be insufficient. A few articles have described additional treatments, such as hemodialysis and fomepizole, to be useful. We present the case of a 23-year-old Caucasian woman who was unconscious at the emergency department after ingesting 75 g of paracetamol via a nasogastric tube. Her serum paracetamol level was 933 mg/L, with metabolic acidosis and an elevated lactate of 9.7 mmol/L. The patient was treated with the standard combination of activated charcoal, sodium sulfate, and N-acetylcysteine. Because of the severity of the intoxication, hemodialysis and off-label fomepizole were added to the standard treatment plan. Serum paracetamol level showed an accelerated decrease during hemodialysis and fomepizole. The patient recovered without signs of hepatotoxicity and seven days after the paracetamol ingestion, she was discharged from hospital. We suggests that there is a role for hemodialysis and fomepizole in the successful treatment of a massive paracetamol overdose.

Keywords: Paracetamol overdose; N-acetylcysteine; Hemodialysis; Fomepizole

Introduction

Due to its widespread availability, paracetamol (acetaminophen) is often involved in intentional overdose; resulting in roughly 2,600 hospitalizations per year in the United States [1]. Gastrointestinal decontamination and administration of N-acetylcysteine (NAC) are the mainstays of paracetamol overdose treatment [2]. For massive overdoses, treatment with NAC alone may be insufficient. Additional treatments such as hemodialysis and fomepizole may be of added value in the treatment of severe overdose [3-7]. However, few articles have described the combination of NAC, hemodialysis and fomepizole. In this case report, we present a comatose patient with massive paracetamol overdose who was successfully treated with NAC, hemodialysis and fomepizole.

Case

A 23-year-old woman was brought to the emergency department (ED) by her partner 90 minutes after ingesting 75 grams of paracetamol. She had taken the first 25 grams orally; the remaining 50 grams were in the form of effervescent tablets, which she had dissolved in a bowl before self-administering with a syringe through her nasogastric tube (NGT). According to her partner, no other drugs were ingested. Her medical history included gastric bypass surgery, an eating disorder for which she received nutrition

through a NGT, autism spectrum disorder, post-traumatic stress disorder, and a history of drug abuse.

On initial assessment she was underweight (BMI 18.0) and unconscious (Glasgow Coma Score 3), and had a blood pressure of 77/31 mmHg, a heart rate of 100 bpm, a respiratory rate of 17/min, SpO2 94% with 2 L/min oxygen flow on a nasal cannula, and a temperature of 35.5°C. Arterial blood gas analysis showed metabolic acidosis (pH 7.23, pCO22.6 kPa, HCO3- 9 mmol/L) with a serum lactate of 9.7 mmol/L. Laboratory results showed hypokalemia (3.1 mmol/L), hypophosphatemia (0.56mmol/L), slightly elevated hepatic enzymes (AST 94 U/L, ALT 60 U/L) and a prolonged prothrombin time (15.1 s). The serum paracetamol concentration was 933 mg/L (therapeutic range 10-20 mg/L, toxic level > 150 mg/L and >75 mg/L with risk factors (liver failure, alcohol abuse and malnutrition) four hours after ingestion). The patient was intubated and transferred to the intensive care unit (ICU). Activated charcoal and sodium sulfate were given through the NGT. Two hours after paracetamol ingestion, NAC 150 mg/kg was administered intravenously over 15 minutes, followed by a 75 mg/kg infusion every four hours according to Dutch protocol [8].

Because of the high paracetamol concentration, it was decided to start hemodialysis in accordance with the EXTRIP guidelines.9 At this point, the concentrations of serum paracetamol and lactate were 675 mg/L and 7.9 mmol/L. Five hours and thirty minutes after ingestion, a double lumen central venous catheter was inserted in the left jugular vein. A Nipro ELISIO 21H dialyser was used, with a dialysate flow of 500 mL/minute and a blood flow of 300 mL/minute. During hemodialysis, the dosage of NAC was doubled to 150 mg/kg every four hours, to compensate for the NAC being cleared by dialysis. After 90 minutes of dialysis, the serum paracetamol and lactate concentrations were decreased to 273 mg/L and 1.4 mmol/L, respectively.

After consultation with the National Poisons Information Centre of the Netherlands, intravenous fomepizole was added to the treatment. Seven hours after paracetamol ingestion, a loading dose of 15 mg/kg was given, followed by a continuous infusion of 1 mg/kg/hour for three hours.

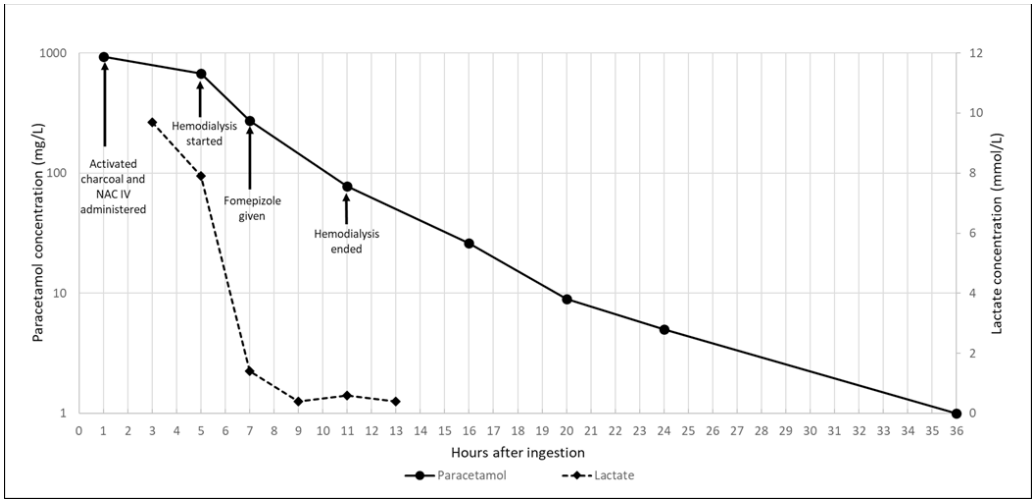

Figure 1: Paracetamol and lactate concentrations over time after ingestion of 75 gram of paracetamol with the timing of treatment. Y-axis describing paracetamol concentrations is logarithmic. NAC, n-acetylcysteine; IV, intravenous

Figure 1 shows the paracetamol and lactate concentrations over time. The half-life of paracetamol was 7.5 hours before hemodialysis, and 2.7 hours after hemodialysis and fomepizole treatment. Since the paracetamol level was decreased by 90% with a level below the normal cut-off for liver toxicity, no repeat dose of fomepizole was given, and dialysis was discontinued after six hours. NAC therapy was continued for 48 hours.

The patient regained consciousness and was extubated 15 hours after paracetamol ingestion. Hypophosphataemia and hypokalemia were both corrected with infusions. Four days after ICU admission, the patient was discharged to the nursing ward. During follow-up, liver enzymes and coagulation tests normalised. The patient did complain about upper abdominal pain for which an ultrasound was performed, which showed no signs of hepatic pathology. Seven days after the paracetamol ingestion, the patient was discharged.

Discussion

We present a case of a young woman who took a massive paracetamol overdose, becoming unconscious and developing severe lactic acidosis within three hours after ingestion via a NGT. Because of these life-threatening events and the extremely high paracetamol concentration, we started hemodialysis and administered intravenous fomepizole in addition to standard care with NAC and activated charcoal. This resulted in a lower paracetamol half-life and no development of hepatotoxicity. The patient recovered well and went home in good condition seven days after admission.

The early onset of coma and lactic acidosis made this case unusual. Typical presentations of an acute paracetamol overdose are nausea, lethargy and malaise, but patients can also remain asymptomatic. In untreated paracetamol overdose, encephalopathy and lactic acidosis may develop three to four days after ingestion due to hepatic failure. However, in cases of massive overdose (ingestion of > 500 mg/kg), patients may develop mitochondrial dysfunction before hepatic failure occurs, resulting in lactic acidosis and an altered state of consciousness within several hours [10-12]. Besides the sheer scale of the overdose in our case, two other factors may have contributed to the rapid rise in the serum paracetamol: first, the paracetamol was dissolved and administered through a NGT, and second the patient had a history of gastric bypass surgery. Chen et al. reported increased rates of absorption and higher peak concentrations of paracetamol after gastric bypass surgeries [13]. The combination of these factors may have facilitated the dumping of the drug into the small intestines, accelerating the absorption.

The standard treatment of paracetamol overdose consists of activated charcoal with sodium sulfate (gastrointestinal decontamination), and administration of NAC. Guidelines for paracetamol overdose recommend starting gastrointestinal decontamination within 4-6 hours after ingestion to lower the rate of absorption in the gastrointestinal tract [9].

NAC directly enhance the elimination of paracetamol. Under normal conditions, paracetamol is metabolized to glucuronide and sulfate metabolites by uridine 5'-disphospho-glucuronosyltransferase and sulfotransferase. Such metabolites are excreted by the urine and are non-toxic. A small amount of paracetamol is converted by CYP2E1 to N-acetyl-p-benzoquinone imine (NAPQI), a toxic metabolite, which is directly bonded to glutathione for detoxification. In overdose, glutathione becomes exhausted and NAPQI concentration increases, which induces mitochondrial oxidative stress and hepatocyte necrosis [14]. NAC provides cysteine for replenishing hepatic glutathione stores and may directly reduce NAPQI concentrations by the sulfation pathway [2].

Following the Rumack-Matthew nomogram, administration of NAC was indicated and we followed the Dutch guidelines for the dosage. This consists of a loading dose of 150 mg/kg for the first hour, followed by 75 mg/kg for four hours [8].This dose is higher than the NAC dose recommended in some international guidelines [15-17].

The high concentration of paracetamol and the severe clinical condition of the patient prompted us to look at additional treatment options. In some reports of massive overdose, hemodialysis has been used to remove paracetamol from plasma and resolve the acidosis [3-6].

The EXTRIP workgroup, responsible for recommendations for extracorporeal treatment (ECTR) in drug overdoses, recommends ECTR when the paracetamol concentration is higher than 900 mg/l, NAC already is administered and the patient has an altered mental status with a metabolic acidosis and elevated lactate. All of these conditions were present in our case [9,20].

The normal half-life of paracetamol is 1.9-2.5 h.20 As described above, we observed a higher half-life in our patient before hemodialysis than after dialysis (7.5 h vs 2.7 h). These findings suggest that hemodialysis eliminated enough paracetamol to restore the glutathione concentration and allow the recovery of the normal pathways for paracetamol metabolism. Lower concentrations of toxic metabolites may have prevented hepatotoxicity and nephrotoxicity.

During hemodialysis, paracetamol was not the only compound eliminated. Ghanoum et al. reported that NAC is also dialyzable, at an even higher rate than paracetamol [21]. The dose of NAC was doubled during hemodialysis to compensate for the loss.

Because of the severity of the overdose and the low risk of side effects, fomepizole was added to the treatment. Fomepizole is developed as a competitive inhibitor of alcohol dehydrogenase (ADH) and is mainly used for ethylene glycol and methanol

poisoning. In addition, fomepizole acts as an inhibitor of CYP2E1, the enzyme responsible for the conversion of paracetamol into the toxic metabolite NAPQI [22]. Moreover, fomepizole inhibits c-Jun N-terminal kinase (JNK) activation and hence decreases the dysfunction and oxidative stress to the mitochondria [23]. These mechanisms of action, observed both in mice and human hepatocytes, suggest that fomepizole could be an antidote to paracetamol. In a crossover trial evaluating the effect of fomepizole on the metabolism of paracetamol, five healthy volunteers received a non-toxic, oral paracetamol dose of 80mg/kg, both with and without fomepizole infusion of 15 mg/kg plus 10 mg/kg twelve hours later. This significantly reduced the amount of oxidative plasma metabolites in the urine compared with paracetamol alone [24]. In the last decade, some studies have reported on the use of fomepizole in the treatment of massive paracetamol overdose. Pourbagher-Shahri et al. summarized fourteen case reports and a small series of studies where fomepizole was added to the treatment of paracetamol overdose. Ten cases were treated with NAC and fomepizole and eight cases received NAC, hemodialysis and fomepizole. Thirteen cases received one dose of fomepizole and nine cases two or more doses. All patients survived the intoxication, except one who suffered from a diffuse axonal injury and died [25].Pourbagher-Shari et al. concluded that fomepizole can be considered as an adjunct to therapy to NAC in selected cases, although the clinical benefit beyond NAC monotherapy remains to be clearly defined. Also in our case, it remained unclear what the added value of fomepizole was. Thus, further research on the role of fomepizole in the treatment of a paracetamol overdose is needed. Two additional case reports described a higher clearance of fomepizole during hemodialysis [26]. For that reason, fomepizole was continued at a dosage of 1 mg/kg/h throughout hemodialysis in our patient.

During treatment, our patient developed hypokalemia and hypophosphatemia which were both corrected with supplementation. These abnormalities might be related to the paracetamol ingestion. Pakravan et al. found a dose-dependent relationship between paracetamol and the fractional excretion of potassium in the urine. They proposed that paracetamol increased aldosterone action through cyclo-oxygenase inhibitor (COX) -mediated renal vasoconstriction. Additionally, the production of vasodilator prostaglandins might be reduced [27]. However, these mechanisms have not been conclusively defined; other studies have also associated paracetamol poisoning with low serum phosphate levels and renal loss of phosphate, without offering a conclusive explanation [28].

In conclusion, this case report suggests that there is a role for hemodialysis and fomepizole in the successful treatment of a massive paracetamol overdose. Hemodialysis was added to the treatment according to EXTRIP guidelines. The off-label use of fomepizole, which presumably inhibits the conversion of paracetamol to NAPQI, was based on previous case reports.

Declaration

Authors' contributions: BN and HO contributed to the design of the study and writing of the manuscript. AS and MB reviewed the manuscript critically for important intellectual content and revised part of the manuscript. All authors reviewed the final manuscript and approved the final version of the article.

Competing interests: The authors declare that they have no competing interests.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethics approval and consent to participate: Institutional Review Board or Ethics approval was not needed for this manuscript. Informed consent for publication was obtained from the patient prior to submission of this manuscript.

Availability of supporting data: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Funding: There is no specific funding for this work.

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