Accidental Paracetamol Poisoning: A Neonatal Case Report

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Abstract

Cases of liver failure following paracetamol poisoning in newborns are uncommon. We report the case of paracetamol intoxication secondary to the highest single dose ever accidentally administered intravenously at our knowledge in the neonatal population. The patient was a pre-term-born girl from a twin pregnancy. The mistake was quickly reported and treatment with N-acetylcysteine (NAC) was initiated within an hour of administration of the toxic dose. The newborn remained clinically asymptomatic and hepatic tests remained within the normal limits for age during the monitoring in the pediatric intensive care unit (PICU). Due to an immature liver at this age, the pharmacokinetics of the drug differs compared to older children or adults. Neonates appear to be less sensitive to paracetamol intoxication. Paracetamol poisoning management is mainly based on studies conducted in adults and does not differ in children including newborns. We discuss the limitations of this approach and its prospects through a literature review.

Keywords: Neonatal; Intensive care unit; New Borns; Paracetamol

Abbreviations

NAC: N-Acetyl cysteine
PICU: Pediatric Intensive Care Unit
NAPQI: N-acetyl-p-benzoquinone-imine
GOT: Glutamate Oxaloacetate Transaminase
GPT: serum Glutamic Pyruvate Transaminase
INR: International Normalized Ratio

Introduction

Paracetamol intoxication is the leading cause of liver failure in the pediatric population, although neonatal case reports are rarer [1-3]. The sensitivity of neonates to overdose is poorly understood and the toxic dose is uncertain, which is why its treatment is based on pharmacokinetic studies and established protocols in adults [1,4]. Nevertheless, some pathophysiological evidence and studies suggest increased tolerance to paracetamol overdose in newborns [3,5-8].

Paracetamol overdose often follows accidental intravenous administration [1,4,9]. Most of the time it is the result of an error in converting mg to mL. Generally, doses are toxic if they correspond to 10 times the therapeutic dose or if the drug is administered cumulatively for more than two days [3].

We describe a case report of accidental paracetamol intoxication following the highest dose ever reported in pediatrics. We also discuss, through a literature review, the physiopathology, the management of paracetamol intoxication, and its future perspectives, notably concerning the use of new biomarkers.

Case report

This is a case report of a female infant who was born from a monochorionic diamniotic twin pregnancy by cesarean section at 34 + 2/7 weeks for suspected twin-to-twin transfusion syndrome. She was the first twin with a birth weight of 1955g (P25-50). The
immediate newborn assessment was normal with an Apgar score of 9/10/10. Both newborns were transferred to the neonatal unit for further management of their prematurity.

Within the first two hours of life, the newborn received an intravenous dose of paracetamol intended for maternal analgesia due to mishandling of peripheral catheters. This mistake was detected after the complete injection of the dose of 1000 mg, equivalent to 511mg/kg, which is 51 times the normal dose for the child’s age and weight.

Treatment with NAC was initiated within an hour at a dose of 150 mg/kg/24h according to the standard treatment protocol used in Belgium for paracetamol poisoning. The child was transferred to the PICU for monitoring.

Blood samples were taken at H1-H4-H8-H24-H48-H72 and H96 after the event (Table 1, Figures 1 and 4). Paracetamol blood levels at 4 hours after the administration of the toxic dose were measured at 431.5 μg/mL (Table 1 and Figure 2). Liver enzymes and coagulation tests remained within the normal limits for the age and the term of the baby (Table 1 and Figure 2-4). The infant did not show any digestive or neurological symptoms during her stay in the PICU. Treatment with NAC was continued until complete clearance of paracetamol on the 4th day of life (Table 1 and Figure 1).

<table>
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<th>Normal Values</th>
<th>Unit</th>
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<th>H4</th>
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<th>H24</th>
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<td>U/L</td>
<td>&lt;5</td>
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<tr>
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<td></td>
<td></td>
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<td>2.9</td>
<td>2.1</td>
<td>1.9</td>
<td>1.3</td>
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<td>245.4</td>
<td>180.3</td>
<td>94.1</td>
<td>11</td>
<td>&lt;5</td>
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Table 1: Blood tests

Figure 1: Plasma Concentrations of acetaminophen in time.
Figure 2: Plasma Concentrations of GOT and GPT in time.

Figure 3: INR in time.
Discussion

In newborns, the liver is immature. During the metabolism of paracetamol in a healthy neonate, the sulfation pathway is more active than glucuronidation. As a result, glutathione reserves are higher, and the liver is, therefore, less rapidly susceptible to drug overdosing [1,3,5,10-13]. In addition, neonates have less cytochrome P450, which means less production of hepatotoxic N-acetyl-p-benzoquinone-imine (NAPQI) [1,3,5,14-16].

However, the half-life of the drug is higher (3.5 hours vs 1.5 to 2 hours) [1,3-5,10,17] and cases of liver failure have been reported at this age [3-5]. These involve cases of cumulative administration over a prolonged period of more than 2 to 3 days [3,18]. For these reasons, we remain vigilant in cases of paracetamol poisoning for this age.

According to the literature, the effective dose of paracetamol should correspond to a plasma concentration of 10 mg/L [1]. In neonatology, to achieve this, a loading dose of 20 to 30 mg/kg is required, followed by a maintenance dose of 10 to 15 mg/kg every 6 or 12 hours, depending on the term and route of administration [1,12-14]. In pediatrics, the potentially lethal dose is estimated to be 150 mg/kg/day. However, it is rare to encounter hepatic toxicity at doses lower than 200 mg/kg/day in newborns [2,8,12,13]. Existing studies on the pharmacokinetics of paracetamol for this age, especially in preterm infants are limited and insufficient to conclude on an adequate and more term-specific paracetamol dosage, especially regarding intravenous administration. Despite this fact, there is an increase in the use of paracetamol by this route of administration [5,19-21].

The pathophysiological mechanism of paracetamol poisoning involves the triggering of hepatocyte apoptosis or necrosis following the accumulation of NAPQI, causing an increase in oxidative stress and mitochondrial dysfunction [5,22]. The treatment with NAC improves sulfation performance and reduces NAPQI to acetylated paracetamol while avoiding glutathione depletion [1,3,23,24]. NAC also improves the clinical status of a patient whose liver failure is already established by acting as an antioxidant, improving hepatic blood flow, hepatic oxygen consumption, and reducing possible cerebral edema [3,24]. NAC appears to be a safe drug overall, except for the occurrence of non-IgE-mediated anaphylactic reactions in some cases during intravenous administration [17,22].

Treatment of paracetamol intoxication is started when plasma concentrations of acetaminophen measured 4 and 8 hours after poisoning are above the risk line established in the 1975 Rumack-Matthew nomogram, which starts at 150 or 200 μg/mL depending on the country [1,3,25-27], or if there is a perturbation of liver enzymes [3,27,28]. In Belgium, if the time of intoxication is unknown, it is indicated to treat if the delivered dose exceeds 150 mg/kg [27]. This approach is based mainly on studies conducted in adults and is extrapolated to children including newborns [1,5]. The decision to stop the treatment depends on the clinical and biological monitoring of the patient which includes hepatic enzymes and liver function [3,24,29-31].

The Rumack-Matthew nomogram considers the plasma concentration of acetaminophen over time after ingestion up to only 24 hours, which raises doubts about the management of patients having to be managed more than a day after the toxic dose.
administration. Additionally, it is only valid for cases of single ingestion and not cumulative [22]. The gold standard used to assess liver damage is the measurement of liver enzymes: glutamate oxaloacetate transaminase (GOT) and serum glutamic pyruvate transaminase (GPT). GPT is less specific to the liver than GOT. Furthermore, GPT and GOT levels rise only 8 hours after toxic ingestion of paracetamol, corresponding to the threshold time for treatment with NAC. The International Normalized Ratio (INR), which evaluates coagulation, is a better prognostic marker for liver damage than transaminases but is only disturbed in severe cases and late stage [22].

When managing acetaminophen poisoning, we face three major problems: the lack of specificity and sensitivity of biomarkers used in practice for the diagnosis and monitoring of liver damage during NAC treatment following acetaminophen poisoning, the limitations of the Rumack-Matthew nomogram, and the inter-individual variability of patients hepatotoxic response (variations in glutathione reserves due to malnutrition/fasting or age, polymorphism of paracetamol metabolism based on genetics or age, increased activity of CYTP450 induced by the intake of certain drugs or depending on age) [22].

In parallel with the biomarkers already used to assess liver damage, additional more sensitive, and specific biomarkers are being evaluated for future clinical use in paracetamol intoxication [3,6,22]. Unfortunately, none of the new biomarkers have been evaluated to date in newborns and infants [22].

These biomarkers include protein derivatives of acetaminophen (acetaminophen-cysteine product and multiplication product of acetaminophen-aminotransferase), circulating mitochondrial content (DNA, glutamate dehydrogenase, argininosuccinate synthase, carbamoyl phosphate synthase), substrates of mitochondrial transporters during beta-oxidation of fatty acids (acylcarnitines), markers of hepatocyte necrosis or apoptosis (HMGBl, keratin-18, circulating nuclear DNA fragments), and miR122 (liver-specific circulating RNA) [3,5,22]. They could all be used to diagnose liver damage quickly, except for mitochondrial biomarkers and keratin-18, which rise only 8 hours after toxic drug ingestion. Protein derivatives of acetaminophen would be the most specific for liver damage following intoxication. MiR122 is the hepatotoxicity biomarker that rises the fastest. It is also easily measurable in capillary blood. Although it is not specific to a lesion following acetaminophen poisoning, it would be easily implemented in clinical practice for the evaluation of liver damage and has already been evaluated in pediatrics. They could all be used during NAC treatment monitoring, just like INR and transaminases, and serve as prognostic biomarkers unlike transaminases [22].

Conclusion

Acetaminophen poisoning is the leading cause of liver failure in pediatrics, although neonatal cases are rarely reported. Toxic doses are most often accidentally administered by intravenous route. The management of an overdose is mainly based on pharmacokinetic studies and established protocols in adults and is extrapolated to pediatrics including neonatology. In this context, we report a case of a prematurely born girl who accidentally received the highest dose ever reported in pediatrics, 51 times the dose normally administered for the newborn’s age and weight. Fortunately, thanks to early treatment with NAC, the child remained asymptomatic and liver tests remained normal for the age during the monitoring in the pediatric intensive care department. Treatment was continued until the complete disappearance of acetaminophen in the blood. Although newborns are less susceptible to acetaminophen overdose due to their immature livers, we remain vigilant regarding their management. This article highlights the importance of prompt management in case of acetaminophen poisoning. New management perspectives with the use of new biomarkers are being studied to improve monitoring and early detection of liver damage in acetaminophen poisoning. It is therefore crucial to continue to improve our knowledge regarding the pathophysiology and management of this condition in neonates to improve it in the future.

Article Summary

Liver failure due to paracetamol poisoning in newborns is uncommon. This is the case of the highest accidental intravenous dose ever reported. Prompt N-Acetylcysteine treatment prevents symptoms and liver damage. We discuss the pharmacokinetics, the management of paracetamol poisoning in neonates, and its future perspectives.

What’s Known on This Subject

The management of neonatal paracetamol poisoning follows adult protocols. The understanding of neonatal sensitivity to the poisoning is limited and the toxic dose is uncertain. N-acetylcysteine is used for its treatment. The neonatal pharmacokinetics of paracetamol differs. Future perspectives include biomarker exploration for improved management.

What This Case Report Adds

A case report detailing the highest paracetamol poisoning in neonates, coupled with a literature review, contributes valuable information to the existing literature by enhancing understanding, highlighting unique aspects, and identifying potential avenues for further research.
Acknowledgments

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