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Severe Acetaminophen Overdose in a Premature Neonate: A Potent Pharmacological Benefit of Immaturity?

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ABSTRACT

A preterm infant, born at 27.2 weeks of gestation and treated for persistent patent ductus arteriosus, received inadvertently a total dose of 780 mg/kg Acetaminophen (APAP) intravenously in 13 divided doses over 3 days, instead of 60 mg/kg/day as recommended. APAP concentration was 256 mg/l after the 13th injection, when intravenous N-Acetylcysteine (NAC) administered as continuous infusion was started and administered during 3 days. Liver function tests remained normal, only a lactic acidosis was transiently observed. In contrast to overdoses in older children and adults associated with high risk of severe hepatoxicity, favorable outcome, most frequently reported in neonates, might be explained by metabolic immaturity protecting premature neonates from hepatic failure and death.

INTRODUCTION

Acetaminophen (APAP, N-acetyl-para-aminophenol, also named paracetamol,) is a well-known antipyretic and analgesic drug, currently used both in adults and pediatric patients. Additional indication includes treatment of Patent Ductus Arteriosus (PDA) in premature newborns. APAP overdosing results in hepatotoxicity and liver failure in adults and paediatric patients and a few cases have already been reported in neonates. We report here a major intoxication to APAP administered to treat a PDA in a very preterm baby, who received N-acetylcysteine (NAC). In agreement to previous reports [1], adapted care allowed favorable outcome and a "potential benefit" of metabolic immaturity may be discussed.

CASE REPORT

A preterm male neonate was born at 27 Gestational Weeks (GW): his 30 year-old mother was a second gest. Both parents are Polynesian, without known consanguinity. Pregnancy was marked by a gestational diabetes requiring insulin. Rupture of membranes occurred and maternal intramuscular corticosteroid (betamethasone: 2 mg) was administered on June 17 and 18, 2021. A caesarian section was required for metrorrhagia. At birth, the neonate weighted 950 g, length was 36 cm and head circumference was 26 cm, Apgar score was 10/10 at one and five minutes. He needed nasal continuous positive airway pressure with 30% oxygen and surfactant was administered by less invasive surfactant administration technique in the first 2hours of life. He was rapidly put on biphasic mode of ventilation with 21% oxygen. On day 1, the echocardiogram showed a significant persistant PDA, analyzed as

deleterious for hemodynamic adaptation. APAP was started at the daily dose of 60 mg/kg QID (four times daily), administered for 3 days resulting in a cumulative dose of 780 mg/kg APAP.

During that period, the neonate appeared uncomfortable, with a large abdominal distension but hemodynamics and breathing were stable. He was empirically treated with antibiotics (cefotaxime, gentamycin, vancomycin and metronidazole) and total parenteral nutrition for suspicion of enterocolitis. He also received intravenous sodium bicarbonate for metabolic acidosis. The prescription error was evidenced 7 hours after the 13th dose (given for abdominal pain) and acetaminophen plasma concentration was 256 mg/L(day 4).Intravenous NAC was started 10 hours after the last dose: 150 mg/kg was administered during the first hour and then 50 mg/kg over4 hours, 100 mg/kg over16 hours, and 100 mg/kg/24h between 21 and 62 h. Sixty-six hours after NAC initiation, APAP concentration was 8.2 mg/L (Figure 1). Liver function tests were monitoring from neonatal days 1 to 8, the higher values were observed on day 5: ASAT and ALAT were 28 and 7 UI/L, total/conjugate bilirubin were 91/7 mg/L and lactates were 589 mg/L. All biomarkers were in the normal range at day 8. He was discharged at the post-natal age of 2 months, weighing 2200g , clinical examination and biological markers were normal for age. Follow-up confirmed favorable outcome at the age of 6 months.

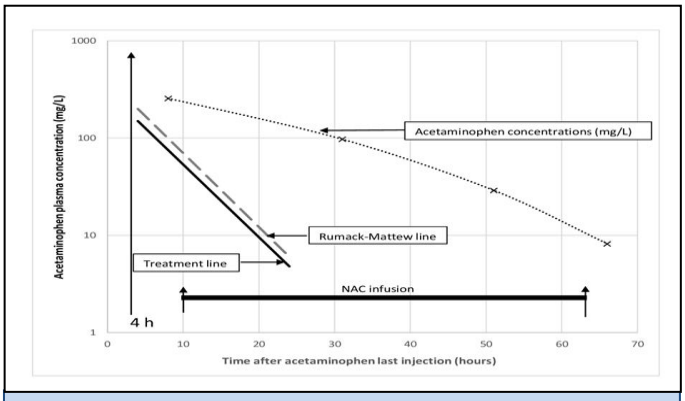

Figure 1: Acetaminophen plasma concentrations versus time during N-acetylcystein administration included in the Prescott toxicity diagram.

DISCUSSION

The observation of a premature neonate, who received the higher dose ever reported of780 mg/kg APAP over 3 day is reported.APAP concentration reached 256 mg/l and treatment with NAC was initiated. Outcome was favorable without any hepatotoxicity. APAP is recommended to treat mild to moderate pain and fever in children and neonates [2]. Treatment schedule is defined in many guidelines, as APAP overdosing, may result in hepatotoxicity and hepatic failure, both in adults and children [3-6]. The maximum recommended therapeutic dose of APAP is 50–75mg/kg/day in children [7].

In addition to previous indications, APAP is administered in neonates to facilitate closure of the PDA. APAP was shown to be effective at the dose of 15 mg/kg/6h during 3 days, resulting in a total APAP dose of 180 mg/kg. Additional data suggest that paracetamol is as effective as ibuprofen and indomethacin in closing PDA. It is also reported to be at lower risk of renal dysfunction than anti-inflammatory drugs. Prophylactic use is also discussed. However, as studies gave conflicting results, additional data are required to confirm efficacy as well as short and long term safety in this neonatal indication [8-12].

In our observation, overdosing was confirmed by the toxic APAP plasma concentration using the Prescott diagram. NAC was administered as antidote and associated with the close monitoring of APAP concentrations [13,14]. Such high exposure did not result in hepatotoxicity or liver failure and outcome was favorable.

Few cases of APAP overdose have been reported in neonates and recently reviewed by Locci and co-authors:12 neonates received high total daily doses, either IV/IM (n=6) : highest dose: 445/211 mg/kg, or orally (n=6): highest dose:266 mg/kg .They were either term or preterm (27 and 28 GW). When reported, overdose was documented by high paracetamol concentrations (n=5/12).When reported, transaminases remained normal (n= 4/12) or were elevated(n=3/12). They all received NAC and full recovery or normalization after NAC occurred in all patients [1]. One additional neonatal overdose was recently reported : paracetamol concentration 19.5 h post-last dose was 381 µmol/L and 236 µmol/L, 9 h later, but liver tests remained normal [15]. Loci [1] also analyzed additional overdoses in infants 2 to 11 months (n=5)complicated with high hepatic enzymes in all cases and encephalopathy in two cases.

Our patient was at even higher risk as he received a high daily dose intravenously, repeatedly over 3 days, this resulted in a

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cumulative dose of 780mg/kg. However, clinical symptoms remained moderate and nonspecific, abdominal distension with lactic acidosis was initially interpreted as enterocolitis and treated symptomatically, administration of NAC allowed a regular decrease in acetaminophen concentrations in 3 days.

Such favorable outcome reported in neonates might, at least in part, be related to the complex metabolism of APAP and the potential impact of hepatic immaturity at birth, even higher in premature than term neonates (Figure 2). At therapeutic doses, APAP is highly metabolized in adults and children by hepatic phase 2 sulfation and glucuronidation. Less than 10% is metabolized by the CYP system (predominantly CYP2E1 and CYP3A4) to N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive intermediate metabolite responsible for APAP toxicity. This toxic metabolite requires gluthation detoxification to avoid toxicity. Conjugation of NAPQI to the sulfhydryl group of glutathione (GSH) occurs through its binding to GSH to form APAP-GSH, excreted in urine as non-toxic cysteine and mercaptopuric acid conjugates. Excess NAPQI eventually depletes GSH stores, resulting in formation of protein adducts and toxicity [7].

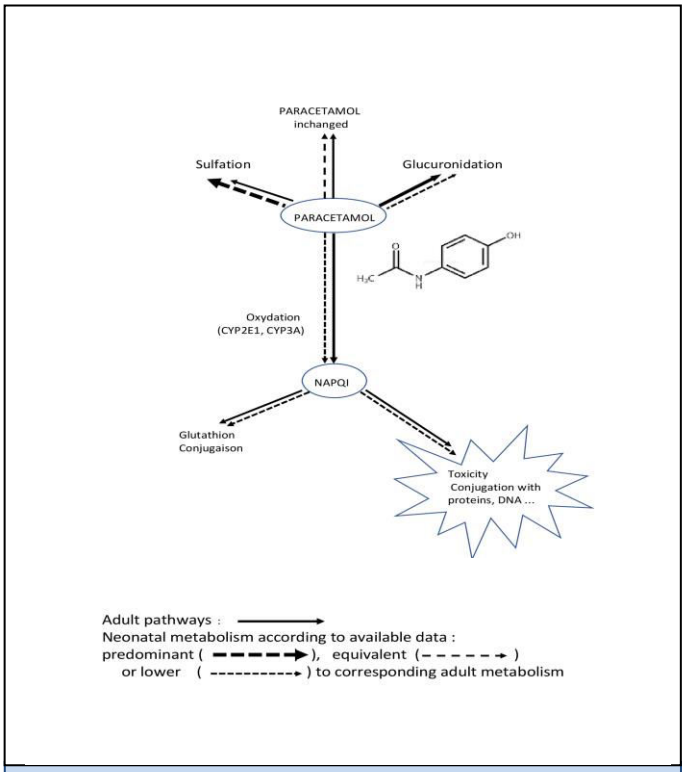

Figure 2: Metabolic pathways of acetaminophen in adults and neonates.

In neonates compared to children and adults, APAP clearance is much lower and increases while half-life decreases with gestational age [16-18]. Few studies have addressed the maturation of APAP elimination: the percentageof the dose excreted in the urine as APAPsulfate is higher in neonates (0-2 days old) and children (3-9 year old) than in 12-year-old children and adults [19]. Additional data showed that, where as glucuronidation matures during the first 2 years of life, sulfation shows a different developmental pattern with higher expression of sulfotransferases (SULT1A1 and SULT2A1) in infants and young children compared to adults. Consequently, APAP glucuronidation is low in preterm neonates and increases with age whereas other pathways are of relatively higher importance compared to adults [11,20,21]. During the neonatal period, the fraction of drug undergoing oxidation increases with weight and post-natal age. To our knowledge, metabolism through CYP2E1 and CYP3A4 leading to NAPQI and followed by glutathione detoxification, has not been quantified yet. Indirect arguments are in favor of a very low activity of this oxidation – conjugation pathway as both CPY2E1 and CYP3A4 are classified as “class 3 enzymes”, not expressed during fetal life, increasing slowly postnatally [22-24]. Therefore, the fraction of paracetamol metabolized to NAPQI is expected to be small, relative to the amount conjugated by glutathione. Such metabolic immaturity even higher in premature neonates, is potentially involved in the limited APAP hepatotoxicity, even when overdosing is important. Indeed, previous case reports and the pharmacokinetics of APAP reveals that fortunately its toxicity is low in preterm infants [1]. Because of conflicting results, this hypothesis of a low production of NAPQI in immature neonates remains to be confirm [15].

CONCLUSION

APAP is metabolized by conjugation and oxidation - detoxification reactions. The equilibrium between these pathways differ between adults and both neonates and young infants. Our case report confirms that, even with very high APAP overdosing, favorable outcome is reported in preterm neonates, when NAC is administered early. The hypothesis of neonatal metabolic immaturity characterized by a limited fraction of drug undergoing oxidation to the toxic NAPQI

metabolite and resulting in limited hepatotoxicity needs to be confirmed.

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