Drug-related perinatal damage from the pharmacological point of view

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Abstract

Medications prescribed to the mother during pregnancy make the foetus vulnerable to adverse effects and the same vulnerability is evident in the phase of adaptation to extrauterine life, particularly delicate in preterm newborns. Among different tissues, the liver and the kidney are particularly sensitive to drugs essentially because they are physiologically immature at birth and have an important role in regulating the effects of medicines inside the body with their primary detoxifying functions.

In this minireview hepatic and renal risks related to prenatal and postnatal exposure to paracetamol and NSAIDs have been examined, being these drugs frequently used during pregnancy and in the neonate for their analgesic/antipyretic effects. Moreover, from an analysis of the literature several case reports of neonatal poisoning deriving from transplacentally-acquired overdoses or administration in the first period of life have been reported.

Keywords

Newborn, perinatal damage, paracetamol, NSAIDs.

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Introduction

The liver and the kidney, physiologically immature at birth, are directly involved in regulating the effects of medicines inside the body, being respectively the primary organs responsible for the biotransformation and excretion of the drugs. Therefore, they are particularly at risk of injury after exposure to drugs either given directly to the newborn (acute effects) or taken by the mother during pregnancy (in this case, signs and symptoms may appear acutely or insidiously over time) [1, 2] and a linkage between kidney and liver drug-induced toxicity has been suggested [3].

Marked developmental-related differences in hepatic drug metabolism are evident during foetal and early postnatal life, particularly as regards the expression and function of CYP isoforms and glucuronidation [4] and also maturation of renal function is a dynamic process that begins early during foetal organogenesis and could affect drug response [5].

In neonates, an increased risk of developing adverse effects in relation of these developmental differences has been observed with some drugs such as chloramphenicol and midazolam [6, 7], while in other cases a protection against toxicity is evident [8]. This minireview will be focused on hepatic and renal risks related to prenatal and postnatal exposure to analgesics/antipyretic agents, paracetamol (acetaminophen) and NSAIDs.

Paracetamol

Paracetamol (acetaminophen), the most commonly prescribed drug in paediatric patients for its analgesic and antipyretic effects, is the only agent recommended for use as antipyretic in the newborn and indicated in this paediatric population for mild-to-moderate pain insults deriving from birth trauma, routine nursing or medical cares, congenital abnormalities [9].

Among its advantages, there is the availability of oral and rectal formulations, particularly useful for use in newborns. In addition, i.v. paracetamol is an attractive analgesic for neonatal use in the postoperative period, where enteral paracetamol is not feasible, offering an alternative or supplement to opioid analgesia in term and preterm newborns, where a reduction of opioid-associated side effects is desirable [10].

While paracetamol is well tolerated at therapeutic dose, liver is the most involved organ in paracetamol acute toxicity after overdosage. Most oxidative drug metabolism is concentrated in the centrilobular zone (zone III), the first and most profoundly affected by paracetamol toxicity, due to the local formation of NAPQI. In severe cases, necrosis may extend to zones I and II destroying the entire parenchyma. Factors predisposing to hepatotoxicity include increased frequency of paracetamol dosing, prolonged duration of excessive doses, co-administration of drugs that induce cytochrome P450 enzymes, increased capacity for P450 activation to NAPQI, reduced glutathione availability or decreased capacity for glucuronidation and sulfation [11]. A specific antidote, N-acetylcysteine, is available and serves as a glutathione precursor or substitute.

Among neonates, differences in paracetamol metabolism render it safer as regards risks of hepatic injury. In fact, the potential hepatotoxicity of this drug is dose-dependent and closely linked to its metabolism, markedly different in neonates compared to children and adults [12, 13].

In the adult, a fraction accounting for 20-40% undergoes to sulphation and glucuronidation. Another fraction, ranging from 5% to 15%, is oxidized by some cytochrome P450 isoenzymes (CYP2E1, CYP1A2, CYP3A4 and CYP2A6) resulting in the formation of the highly reactive N-acetyl-p-benzoquinoneimine (NAPQI), toxic for hepatic cells [14]. Glutathione quickly combines with this intermediate and the complex is then converted to non-toxic cysteine or mercaptate conjugates, which are eliminated in the urine [15]. In an overdose situation and in the absence of sufficient cellular stores of reduced glutathione, NAPQI covalently binds to proteins leading to cell death of hepatocytes [16]. In the neonate, the activity of some isoforms of CYP (particularly CYP2D6 and CYP2E1) is thought to be reduced with a minor production of NAPQI [17]. Moreover, the metabolic profile at birth is characterized by sulphation predominating over glucuronidation. In addition, neonates have a greater capacity to synthesize glutathione [18]. In the foetus, CYP2E1, the primary enzyme responsible for the conversion of paracetamol to its hepatotoxic metabolite NAPQI [19], resulted undetectable in first trimester samples but present in fetal liver microsomes from the late second trimester [20].

Prenatal exposure

Usually, reported cases of neonatal poisoning derive from transplacentally-acquired overdoses of
paracetamol, frequently used as analgesic/antipyretic during pregnancy and able to cross the placenta. If the newborn is delivered within 24 hours of maternal overdose, it is less likely to be affected by maternal toxicity and the case resembles that of an oral overdose. Instead, all reported neonatal deaths occurred when the neonate was delivered more than 24 hours after the maternal overdose. Therefore, early treatment of the mother with N-acetylcysteine, able to cross the placenta and provide hepatoprotection to the foetus, is fundamental [21].

From the analysis of the literature, two cases of foetal death due to hepatotoxicity have been reported at 28 weeks’ gestation [22] and 33 weeks’ gestation [23].

In other situations high plasma paracetamol concentrations observed after a maternal overdose (from 20 to 64 g) of the drug did not cause permanent hepatic injury but only a transient elevation of liver enzymes with a normalization after N-acetylcysteine administration [23-27] or postpartum transfusions [28, 29].

In another case of a term newborn delivered within 17 hours from a maternal overdose of 26 g paracetamol, no abnormality was discovered [30].

Postnatal exposure

While at recommended doses paracetamol administration has not been associated with liver injury [12], hepatotoxicity is possible in neonates and infants after intake of a single high dose or multiple excessive doses. However, serious hepatotoxicity or death after acute paracetamol overdose has rarely been reported in neonates, probably due to the slower oxidative metabolism and faster glutathione synthesis [31].

As specified in a previous review [13], some authors reported accidental overdoses of paracetamol in neonates and infants.

In one case of a 55-day-old neonate born at 29 weeks’ gestation, an overdose of paracetamol 136 mg/kg orally resulted in no biochemical evidence of hepatoxicity or long-term sequelae after N-acetylcysteine administration [32].

Instead, neonatal hepatotoxicity (AST 718 IU/L, ALT 978 IU/L) has been reported in a term neonate (41 weeks’ gestation) who presented encephalopathic 5 days following 3 days of oral paracetamol treatment after circumcision, initially at a daily dose of 156 mg/kg and then 78 mg/kg: paracetamol toxicity was successfully treated with a 20 h N-acetylcysteine infusion [33].

Another case regarded a 58-day-old neonate who presented a transient elevation of liver enzymes after a 16.32 mg/kg oral dose with normalization after N-acetylcysteine [34].

A neonate born at 41 weeks’ gestation was accidentally given an intramuscular injection of 211 mg/kg propacetamol (equivalent to 105.5 mg/kg paracetamol) on the first day of life: treated with N-acetylcysteine for 22 h, liver enzymes remained normal during hospitalization and after discharge [35].

Other authors reported the death of an infant who developed acute fatal hepatic failure after an inadvertent duplication of paracetamol prescription [36], while in another infant N-acetylcysteine administration led to a normalization of liver enzymes after an oral overdose [37].

Since the introduction of intravenous paracetamol, incidents of accidental overdoses, mostly involving a 10-fold dosing error, have been widespread and leaded to changes in dosing instructions and guidelines [38]: in Tab. 1 some cases of paracetamol overdoses in newborns and infants are reported.

The first published case regarded the death of a preterm newborn treated accidentally with 70 mg of i.v. paracetamol [39].

Following a prescribing error, a term female newborn was given two 900 mg i.v. doses of propacetamol (307 mg/kg) at 6 h intervals (10 times the routine dose). The error was noted after the second dose and immediately N-acetylcysteine was administered for 16 h: liver function resulted normal [40].

Other authors [41] reported a case concerning one 7-week-old preterm newborn (35 weeks’ gestation) who was treated accidentally with an overdose of 380 mg i.v. paracetamol (146 mg/kg) for routine elective surgery, but did not develop hepatotoxicity.

Two cases of 10-fold accidental overdose with intravenous paracetamol have been reported: the first 5-month-old infant developed hepatic impairment after 520 mg of the drug (75 mg/kg), while a 6-month-old infant was promptly treated with N-acetylcysteine after 300 mg (75 mg/kg) [42].

A preterm newborn (25 weeks’ gestation) was erroneously treated with 500 mg of paracetamol (53 mg/kg) infused intravenously in 1 h: fortunately, the medication error was early discovered and the neonate was immediately treated with N-acetylcysteine [43].

A 8-month-old infant received an overdose of i.v. paracetamol for elective surgery and developed an
acute hepatitis: a treatment with N-acetylcysteine normalized liver parameters within 4 days [44].

Nephrotoxicity and hepatotoxicity can be seen together after paracetamol overdose: renal dysfunction occurs in about 25% of cases with significant hepatotoxicity and in more than 50% of those with hepatic failure [11]. In some cases, renal impairment after acute paracetamol overdose may also occur in the absence of hepatotoxicity [45] and the pathophysiology of this toxicity has been attributed to the local formation of NAPQI that causes tubular necrosis [46], although other mechanisms have been suggested, including a role of prostaglandin synthetase and N-deacetylase enzymes [47]. Some cases of acute tubular necrosis without hepatic failure have been recently reported in children following paracetamol overdose [48, 49], while no case has been referred to neonates.

**NSAIDs**

NSAIDs are used in the perinatal period in the management of obstetrical complications mainly as tocolytic agents, since prostaglandins are important mediators in delivery, stimulating uterine contractions and enhancing cervical ripening [50]. Moreover, these drugs are frequently used in pregnant women for their antipyretic, analgesic and anti-inflammatory properties [51]. In the newborn, NSAIDs are mainly used in the first days of life to favour the closure of patent ductus arteriosus, a common complication of prematurity [52].

The use of NSAIDs during pregnancy has been associated with different effects on the foetus and newborn depending upon the period in which the drugs have been administered. During early pregnancy, congenital anomalies are the greater risk [53], while premature closure of the ductus arteriosus [54], increased incidence of intracranial haemorrhage and necrotizing enterocolitis [55], impaired renal function [56] have been observed during the third trimester of gestation.

NSAIDs may cause renal damage resulting in acute renal failure with or without oliguria, chronic renal failure, significant proteinuria, fluid metabolism alterations, hyperkaliemia [57].

The mechanisms implicated in NSAIDs-induced renal dysfunction in the foetus are likely the same involved during postnatal life and are related to the blockade of the synthesis of prostaglandins, substances that play a prominent role in the processes of adaptation to extrauterine life [58-60], with the immature kidney programmed to depend on glomerular and tubular actions of prostaglandins in the perinatal and neonatal period [61]. In particular, classical NSAIDs cause in different degrees a reversible inhibition of the two major isoforms of the key enzyme involved in the prostaglandin synthesis, cyclooxygenase (COX). The constitutive isoform COX-1 is implicated in the maintenance of normal physiological functions in the kidney comprised the regulation of renal blood flow.

### Table 1. Case reports of i.v. paracetamol overdoses.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Dose</th>
<th>Laboratory data</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>de la Pintière et al., 2003 [40]</td>
<td>Term newborn</td>
<td>900 mg (307 mg/kg)</td>
<td>No alterations</td>
<td>No sign of hepatotoxicity after N-acetylcysteine administration</td>
</tr>
<tr>
<td>Nevin et al., 2010 [41]</td>
<td>Preterm newborn (35 weeks’ gestation)</td>
<td>380 mg (146 mg/kg)</td>
<td>No alterations</td>
<td>No sign of hepatotoxicity</td>
</tr>
<tr>
<td>Beringer et al., 2011 [42]</td>
<td>Infant (5 months)</td>
<td>520 mg (75 mg/kg)</td>
<td>Liver enzymes altered</td>
<td>Normalization after N-acetylcysteine administration</td>
</tr>
<tr>
<td>Beringer et al., 2011 [42]</td>
<td>Infant (6 months)</td>
<td>300 mg (75 mg/kg)</td>
<td>No alterations</td>
<td>Normalization after N-acetylcysteine administration</td>
</tr>
<tr>
<td>Porta et al., 2012 [43]</td>
<td>Preterm newborn (25 weeks’ gestation)</td>
<td>500 mg (53 mg/kg)</td>
<td>No alterations</td>
<td>No sign of hepatotoxicity after N-acetylcysteine administration</td>
</tr>
<tr>
<td>Iorio et al., 2013 [44]</td>
<td>Infant (8 months)</td>
<td>n.i.</td>
<td>Acute hepatitis (AST 24,424 U/l, ALT 12,885 U/l, total bilirubin 3.1 mg/dl)</td>
<td>Normalization after N-acetylcysteine administration</td>
</tr>
</tbody>
</table>
while COX-2 plays an essential role in normal renal development and function [63].

Prenatal exposure

Adverse effects on the foetus and newborn have been reported after prenatal exposure to NSAIDs as a result of the transplacental passage of these agents, with differences depending upon the period of pregnancy during which the drug was taken [64, 65]. Moreover, both the duration of maternal NSAID therapy and the distance between maternal administration and the delivery have been reported to be important factors involved in the development of adverse effects in the foetus [66].

Toxicity associated with antenatal NSAID exposure may affect different organ systems, but renal involvement is particularly important: it has been reported that preterm newborns born to mothers who had used NSAIDs during pregnancy present a 7.4 fold higher risk of developing acute renal failure compared to controls [67].

Taking into account the considerable number of pregnant women treated with NSAIDs, the onset of renal complications is a rare occurrence and risks are minimal when the treatment is of short duration (< 72 h), doses are low and delivery does not take place shortly after treatment [50]. In every case, the risk of neonatal renal failure is high following maternal exposure to NSAIDs when nephrogenesis occurs, while the risk is low or null once nephrogenesis has been completed [68].

Several cases of severe and sometimes irreversible renal failure have been reported in the literature, mainly related to indomethacin foetal exposure, a non-selective NSAID used for many years to prevent uterine contractions [69] and to treat polyhydramnios [70].

The first case of oligohydramnios and transient neonatal anuria associated with maternal use of indomethacin was reported by Cantor et al. [71] and other reports followed. The produced effects ranged from transient acute renal failure [55, 56, 72-75] or prolonged severe renal dysfunction characterized by oligohydramnios and persistent anuria [76] to perinatal/neonatal death [77-81]. Structural alterations of glomerular and tubular districts associated with prenatal exposure to indomethacin have been evidenced during post-mortem examinations, in particular ischemic damage, cortical necrosis fibrosis in the medullary area and loss of differentiation between proximal and distal tubules [82].

As reported in Tab. 2, similar effects on renal function has been reported following the

<table>
<thead>
<tr>
<th>Reference</th>
<th>G.A. at delivery (wks)</th>
<th>Drug</th>
<th>Oligohydramnios/ anhydramnios</th>
<th>Neonatal oligo-anuria</th>
<th>Non-oliguric renal failure</th>
<th>Peritoneal dialysis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alessandri et al., 1994 [84]</td>
<td>35</td>
<td>niflumic acid</td>
<td>+ (n.i.)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>surviving</td>
</tr>
<tr>
<td>Voyer et al., 1994 [85]</td>
<td>37</td>
<td>piroxicam</td>
<td>+ (28 wks)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>neonatal death (day 33)</td>
</tr>
<tr>
<td>Gouyon et al., 1991 [83]</td>
<td>28</td>
<td>ketoprofen</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>surviving</td>
</tr>
<tr>
<td>Fieni et al., 2004 [85]</td>
<td>33</td>
<td>ketoprofen</td>
<td>+ (29 wks)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>surviving, mild RF</td>
</tr>
<tr>
<td>Fieni et al., 2004 [85]</td>
<td>33</td>
<td>ketoprofen</td>
<td>+ (29 wks)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>surviving, mild RF</td>
</tr>
<tr>
<td>Koklu et al., 2006 [87]</td>
<td>34</td>
<td>naproxen</td>
<td>+ (27 wks)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>neonatal death (day 30)</td>
</tr>
<tr>
<td>Phadke et al., 2012 [86]</td>
<td>35</td>
<td>diclofenac</td>
<td>+ (35 wks)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>surviving, mild RF</td>
</tr>
<tr>
<td>Phadke et al., 2012 [86]</td>
<td>35</td>
<td>diclofenac</td>
<td>+ (35 wks)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>neonatal death (day 20)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>diclofenac</td>
<td>+ (36 wks)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>surviving</td>
</tr>
</tbody>
</table>

n.i.: not indicated; RF: renal failure.
administration of other classical NSAIDs during pregnancy (niflumic acid, piroxicam, ketoprofen, naproxen, diclofenac): in some cases a mild transient renal failure has been observed [83-86], while in other cases the exposure to maternal NSAID caused the death of the neonate [86-88].

More recently, despite the poor availability of data, the use of preferential/selective inhibitors such as sulindac, nimesulide and celecoxib has been suggested in the treatment of preterm delivery. While no cases of neonatal renal failure have been reported as regards sulindac and celecoxib, transient acute [89, 90] or permanent renal failure [91-94] have been reported following nimesulide exposure in utero. Histological findings revealed a maldevelopment of glomeruli, abnormal tubular differentiation and interstitial fibrosis [91], confirming the essential role of COX-2 in normal renal development and function.

Postnatal exposure

Usually, in early neonatal life NSAIDs are prescribed to induce the closure of patent ductus arteriosus (PDA), a typical complication of prematurity. Among cyclooxygenase inhibitors, indomethacin and ibuprofen remain the drugs of choice for both prophylaxis and therapy to achieve PDA closure [52]. Other NSAIDs have been tested, but resulted either less effective (aspirin) or more toxic (sulindac, mefenamic acid) [95-97].

NSAID-induced nephrotoxicity is not easy to be defined in the newborn, since these drugs are often administered to subjects with haemodynamic abnormalities and/or electrolyte derangements, important co-factors involved in renal damage. However, evidence has been provided to prove that NSAIDs are capable to induce renal adverse effects [98].

Some authors compared indomethacin with ibuprofen in preterm newborns reporting contrasting results.

In a systematic review comprising 19 studies, Ohlsson et al. [99] detected a proportion of preterm infants with oliguria and lower serum creatinine values significantly lower in the ibuprofen group, data consistent with previous studies showing a greater impairment of renal perfusion in newborns exposed to indomethacin [100-104].

After ibuprofen treatment, other authors reported a renal damage statistically significant, but mild and transient [105-107].

Instead, other studies showed that ibuprofen given to close PDA was associated with renal alterations [108-110]. This is in line with a recent work where the authors underlined the risk of renal impairment for VLBW and ELBW newborns treated with ibuprofen, with a greater renal impairment observed in neonates with the lower weight and gestational age at birth [111].

Conclusions

Medications prescribed to the mother during pregnancy make the foetus vulnerable to adverse effects and the same vulnerability is evident in the first days of life, in the phase of adaptation to extrauterine life, particularly delicate in preterm newborns. This is mainly important at hepatic and renal levels, where the physiological changes related to maturation lead to variability both in efficacy and tolerability of a drug treatment.

As regards drug metabolism, the pharmacokinetic peculiarities of the neonate play a relevant role leading to marked differences compared to children and adults. The immaturity at birth of drug metabolizing enzymes and their rapid developmental changes, at the base of day-by-day differences, correlate with an increased risk of adverse effects reported for some drugs and a protection against hepatotoxicity in other cases [8].

Drug-induced renal injury, even if rare, remains an important clinical problem in the newborn, particularly if preterm [68], and a prenatal exposure to drugs potentially nephrotoxic could influence renal function not only during pregnancy but also after birth. In fact, a possible association between the development of acute renal failure in preterm newborns and maternal drug treatments has been suggested [67], even if the incidence of foetal/neonatal renal impairment remains a controversial issue varying from 1.5 to 20% [1].

All these data clearly indicate the need of a focused and individual approach as a main target for neonatologists, to better clarify the impact of birth and gestational age on drug response during the perinatal period.

Declaration of interest

The Author declares that there is no conflict of interest.

References


Drug-related perinatal damage


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