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Review

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 linkeage 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 leaded 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-infant received an overdose of i.v. paracetamol for elective surgery and developed an

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

Reference	Age	Dose	Laboratory data	Outcome
***Rev Prescrire*, 2010 [39]**	Preterm newborn	70 mg	–	Death
de la Pintière et al., 2003 [40]	Term newborn	900 mg (307 mg/kg)	No alterations	No sign of hepatotoxicity after N-acetylcysteine administration
Nevin et al., 2010 [41]	Preterm newborn (35 weeks' gestation)	380 mg (146 mg/kg)	No alterations	No sign of hepatotoxicity
Beringer et al., 2011 [42]	Infant (5 months)	520 mg (75 mg/kg)	Liver enzymes altered	Normalization after N-acetylcysteine administration
Beringer et al., 2011 [42]	Infant (6 months)	300 mg (75 mg/kg)	No alterations	Normalization after N-acetylcysteine administration
Porta et al., 2012 [43]	Preterm newborn (25 weeks' gestation)	500 mg (53 mg/kg)	No alterations	No sign of hepatotoxicity after N-acetylcysteine administration
Iorio et al., 2013 [44]	Infant (8 months)	n.i.	Acute hepatitis (AST 24,424 U/l, ALT 12,885 U/l, total bilirubin 3.1 mg/dl)	Normalization after N-acetylcysteine administration

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 disfunction 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

[62], 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 2. Nephrotoxic effects due to prenatal exposure to NSAIDs (modified from: Cuzzolin and Fanos, 2012 [2].

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

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 varyng 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

1. Boubred F, Vendemmia M, Garcia-Meric P, Buffat C, Millet V, Simeoni U. Effects of maternally administered drugs on the fetal and neonatal kidney. Drug Saf . 2006;29(5):397-419.

2. Cuzzolin L, Fanos V. Influence of prenatal drug treatments on kidney function during fetal and neonatal life. In: Aranda JV, Fanos V, van den Anker JN (Eds.). Perinatal pharmacology: individualized neonatal therapy. Quartu Sant'Elena (CA): Hygeia Press, 2012.
3. Park SW, Chen SW, Kim M, Brown KM, Kolls JK, D'Agati VD, Lee HT. Cytokines induce small intestine and liver injury after ischemia oe nephrectomy. Lab Invest. 2011;91:63-84.
4. Cuzzolin L. Drug metabolizing enzymes in the perinatal and neonatal period: differences in the expression and activity. Curr Drug Metab. 2013;14:167-73.
5. Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Chatelut E, Grubb A, Veal GJ, Keir MJ, Holford NH. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009;24(1):67-76.
6. Strolin Benedetti M, Whomsley R, Canning M. Drug metabolism in the paediatric population and in the elderly. Drug Discov Today. 2007;12:599-610.
7. de Wildt SN, Kearns GL, Murry DJ, Koren G, van den Anker JN. Ontogeny of midazolam glucuronidation in preterm infants. Eur J Clin Pharmacol. 2010;66:165-70.
8. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology: drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349(12):1157-67.
9. Cranswick N, Coghlan D. Paracetamol efficacy and safety in children: the first 40 years. Am J Ther. 2000;7:135-41.
10. Palmer GM, Chen SP, Smith KR, Hardikar W. Introduction and audit of intravenous paracetamol at a tertiary paediatric teaching hospital. Anaesth Intensive Care. 2007;35:702-6.
11. Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, Leone S. Paracetamol: new vistas of an old drug. CNS Drug Rev. 2006;12:250-75.
12. Allegaert K, Rayyan M, de Rijdt T, van Beek F, Naulaers G. Hepatic tolerance of repeated intravenous paracetamol administration in neonates. Paediatr Anaesth. 2008;18:388-92.
13. Cuzzolin L, Antonucci R, Fanos V. Paracetamol (Acetaminophen) efficacy and safety in the newborn. Curr Drug Metab. 2013;14(2):167-73.
14. Corcoran GB, Mitchell JR, Vaishnav YN, Horning EC. Evidence that acetaminophen and N-hydroxyacetaminophen form a common arylating intermediate, N-acetyl-p-benzoquinoneimine. Mol Pharmacol. 1980;18:536-42.
15. Miller RP, Roberts RJ, Fischer LJ. Acetaminophen elimination kinetics in neonates, children and adults. Clin Pharmacol Ther. 1976;19:284-94.
16. Prescott LF, Roscoe P, Wright N, Brown SS. Plasma paracetamol half-life and hepatic necrosis in patients with paracetamol overdosage. Lancet. 1971;1:519-22.
17. Krumbiegel P, Domke S, Morseburg B, Boehm G, Braun W. Maturation of hepatosomal mono-oxygenation and glucuronidation activities in pre- and full-term infants as studied using the methacetin urine test. Acta Paediatr. 1997;86:1236-40.
18. Van Eyken P, Nemolato S, Faa G, Ambu R. Hepatic injury to the newborn liver due to drugs. Curr Pharm Des. 2012;18:3050-60.
19. Bolt HM, Roos PH, Thier R. The cytochrome P450 isoenzyme CYP2E1 in the biological processing of industrial chemicals: consequences for occupational and environmental medicine. Int Arch Occup Environ Health. 2003;76:174-85.
20. Johnsrud EK, Koukouritaki SB, Divakaran K, Brunengraber LL, Hines RN, McCarver DG. Human hepatic CYP2E1 expression during development. J Pharmacol Exp Ther. 2003;307:402-7.
21. Wilkes JM, Clark LE, Herrera JL. Acetaminophen overdose in pregnancy. South Med J. 2005;98:1118-22.
22. Haibach H, Akhter JE, Muscato MS, Carly PL, Hoffmann MF. Acetaminophen overdose with fetal demise. Am J Clin Pathol. 1984;82(2):240-2.
23. Riggs BS, Bronstein AC, Kulig K, Archer PG, Rumack BH. Acute acetaminophen overdose during pregnancy. Obstet Gynecol. 1989;74:247-53.
24. Stokes IM. Paracetamol overdose in the second trimester of pregnancy: case report. Br J Obstet Gynaecol. 1984;91(3):286-8.
25. Ludmir J, Main DM, Landon MB, Gabbe SG. Maternal acetaminophen overdose at 15 weeks of gestation. Obstet Gynecol. 1986;67(5):750-1.
26. Rosevear SK, Hope PL. Favourable neonatal outcome following maternal paracetamol overdose and severe fetal distress: case report. Br J Obstet Gynecol. 1989;96(4):491-3.
27. Aw MM, Dhawan A, Baker AJ, Mieli-Vergani G. Neonatal paracetamol poisoning. Arch Dis Child Fetal Neonatal Ed. 1999;81:F78.
28. Roberts I, Robinson MJ, Mughal MZ, Ratcliffe JG, Prescott LF. Paracetamol metabolites in the neonate following maternal overdose. Br J Clin Pharmacol. 1984;18:201-6.
29. Lederman S, Fysh WJ, Tredger M, Gamsu HR. Neonatal paracetamol poisoning: treatment by exchange transfusion. Arch Dis Child. 1983;58:631-3.
30. Kumar A, Goel KM, Rae MD. Paracetamol overdose in children. Scott Med J. 1990;35:106-7.
31. Lauterburg BH, Vaishnav Y, Stillwell WG, Mitchell JR. The effects of age and glutathione depletion on hepatic glutathione turnover *in vivo* determined by acetaminophen probe analysis. J Pharmacol Exp Ther. 1980;213:54-8.
32. Isbister GK, Bucens IK, Whyte IM. Paracetamol overdose in a preterm neonate. Arch Dis Child Fetal Neonatal Ed. 2001;85:F70-2.
33. Walls I, Baker CF, Sarkar S. Acetaminophen-induced hepatic failure with encephalopathy in a newborn. J Perinatol. 2007;27:133-5.
34. Muniz AE, Rose SR, Liner SR, Foster RL. Unsuspected acetaminophen toxicity in a 58-day-old infant. Pediatr Emerg Care. 2004;20(12):824-8.
35. Nolent P. Intramuscular injection of propacetamol in a neonate. Arch Dis Child Fetal Neonatal Ed. 2002;87:F155-6.
36. Ebenezer K, Agarwal I, Fleming D. Acute hepatic failure in an infant caused by acetaminophen (paracetamol) toxicity. Ann Trop Pediatr. 2008;28(4):301-3.

37. Kubic A, Burda AM, Bockewitz E, Wahl M. Hepatotoxicity in an infant following supratherapeutic dosing of acetaminophen for twenty-four hours. Semin Diagn Pathol. 2009;26(1):7-9.
38. Dart RC, Rumack BH. Intravenous acetaminophen in the United States: iatrogenic dosing errors. Pediatrics. 2012;129(2):349-53.
39. Injectable paracetamol in children: fatal confusion between milligrams and millilitres. Rev Prescrire. 2010;30:348.
40. de la Pintiére A, Beuchée A, Bétrémieux PE. Intravenous propacetamol overdose in a term newborn. Arch Dis Child Fetal Neonatal Ed. 2003;88:F351-2.
41. Nevin DG, Shung J. Intravenous paracetamol overdose in a preterm infant during anesthesia. Paediatr Anaesth. 2010;20:105-7.
42. Beringer RM, Thompson JP, Parry S, Stoddart PA. Intravenous paracetamol overdose: two case reports and a change to national treatment guidelines. Arch Dis Child. 2011;96(3):307-8.
43. Porta R, Sanchez L, Nicolas M, Garcia C, Martinez M. Lack of toxicity after paracetamol overdose in a extremely preterm neonate. Eur J Clin Pharmacol. 2012;68(5):901-2.
44. Iorio ML, Cheerharan M, Kaufman SS, Reece-Stremtan S, Boyajian M. Acute liver failure following cleft palate repair: a case of therapeutic acetaminophen toxicity. Cleft Palate Craniofac J. 2013;50(6):747-50.
45. Campbell NR, Baylis B. Renal impairment associated with an acute paracetamol overdose in the absence of hepatotoxicity. Postgrad Med J. 1992;68:116-8.
46. Breen K, Wandscheer JC, Peignoux M, Pessayre D. *In situ* formation of the acetaminophen metabolite covalently bound in kidneys and lung. Supportive evidence provided by total hepatectomy. Biochem Pharmacol. 1982;31:115-6.
47. Mazer M, Perrone J. Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations, and management. J Med Toxicol. 2008;4:2-6.
48. Onay OS, Erçoban HS, Bayrakci US, Melek E, Cengiz N, Baskin E. Acute, reversible nonoliguric renal failure in two children associated with analgesic-antipyretic drugs. Paediatr Emerg Care. 2009;25:263-6.
49. Ozkaya O, Genc G, Bek K, Sullu Y. A case of acetaminophen (paracetamol) causing renal failure without liver damage in a child and review of literature. Ren Fail. 2010;32:1125-7.
50. Loudon JA, Groom KM, Bennett PR. Prostaglandin inhibitors in preterm labour. Best Pract Res Clin Obstet Gynaecol. 2003;17:731-44.
51. Østensen ME, Skomsvoll JF. Anti-inflammatory pharmacotherapy during pregnancy. Expert Opin Pharmacother. 2004;5:571-80.
52. Mezu-Ndubuisi OJ, Agarwal G, Raghavan A, Pham JT, Ohler KH, Maheshwari A. Patent ductus arteriosus in premature neonates. Drugs. 2012;72(7):907-16.
53. Ofori B, Oraichi D, Blais L, Rey E, Bérard A. Risk of congenital anomalies in pregnant users of non-steroidal anti-inflammatory drugs: A nested case-control study. Birth Defects Res B Dev Reprod Toxicol. 2006;77:268-79.
54. Auer M, Brezinka C, Eller P, Luze K, Schweigmann U, Schwärzler P. Prenatal diagnosis of intrauterine premature closure of the ductus arteriosus following maternal diclofenac application. Ultrasound Obstet Gynecol. 2004;23:513-6.
55. Norton ME, Merrill J, Cooper BA, Kuller JA, Clyman RI. Neonatal complications after the administration of indomethacin for preterm labor. New Engl J Med 1993;329(22):1602-7.
56. Souter D, Harding J, McCowal L, O'Donnell C, McLeay E, Baxendale H. Antenatal indomethacin-adverse fetal effects confirmed. Aust N Z J Obstet Gynecol. 1998;38(1):11-6.
57. Musu M, Finco G, Antonucci R, Polati E, Sanna D, Evangelista M, Ribuffo D, Schweiger V, Fanos V. Acute nephrotoxicity of NSAIDs from the foetus to the adult. Eur Rev Med Pharmacol Sci. 2011;15(12):1461-72.
58. Langhendries JP, Van Overmeire B. Prostaglandines, anti-inflammatoires non steroidiens (AINS) et rein perinatal: un subtil compromise. In: Guignard JP, Gouyon JB, Simeoni U. Medicaments. Nephrotoxicitè. Insuffisance renale aigue chez le nouveau-nè. Amsterdam: Elsevier, 2001.
59. Knights KM, Tsoutsikos P, Miners JO. Novel mechanisms of nonsteroidal anti-inflammatory drug-induced renal toxicity. Expert Opin Drug Metab Toxicol. 2005;1(3):399-408.
60. Antonucci R, Cuzzolin L, Arceri A, Fanos V. Urinary prostaglandin E2 in the newborn and infant. Prostagland Other Lipid Mediat. 2007;84:1-13.
61. Heymann MA. Prostaglandins and leukotrienes in the perinatal period. Clin Perinatol. 1987;14(4):857-80.
62. Harris RC. Interactions between COX-2 and the rennin-angiotensin system in the kidney. Acta Physiol Scand. 2003;49:15-9.
63. Khan KNM, Stanfield KM, Dannenberg A, Seshan SV, Baergen RN, Baron DA, Soslow RA. Cyclo-oxygenase-2 expression in the developing human kidney. Pediatr Dev Pathol. 2001;4:461-6.
64. King J, Flenady V, Cole S, Thornton S. Cyclo-oxygenase (COX) inhibitor s for treating preterm labour. Cochrane Database Syst Rev. 2005;2:CD001992.
65. Antonucci R, Zaffanello M, Puxeddu E, Porcella A, Cuzzolin L, Pilloni MD, Fanos V. Use of non-steroidal anti-inflammatory drugs in pregnancy: impact on the fetus and newborn. Curr Drug Metab. 2012;13:474-90.
66. Ojala R, Ikonen S, Tammela O. Perinatal indomethacin treatment and neonatal complications in preterm infants. Eur J Pediatr. 2000;159(3):153-5.
67. Cataldi L, Leone R, Moretti U, De Mitri B, Fanos V, Ruggeri L, Sabatino G, Torcasio F, Zanardo V, Attardo G, Riccobene F, Martano C, Benini D, Cuzzolin L. Potential risk factors for the development of acute renal failure in preterm newborn infants: a case-control study. Arch Dis Child Fetal Neonat Ed. 2005;90(6):F514-9.
68. Cuzzolin L, Fanos V, Pinna B, Di Marzio M, Perin M, Tramontozzi P, Tonetto P, Cataldi L. Postnatal renal function in preterm newborns: a role of diseases, drugs and therapeutic interventions. Pediatr Nephrol. 2006;21(7):931-8.
69. Moise KJ, Huhta JC, Sharif DS, Ou CN, Kirshon B, Wasserstrum N, Cano L. Indomethacin in the treatment of premature labor. New Engl J Med. 1988;319:327-31.

70. Mamapoulos M, Assimakopoulos E, Reece EA, Andreou A, Zheng XZ, Mantalenakis S. Maternal indomethacin therapy in the treatment of polyhydramnios. Am J Obstet Gynecol. 1990;162(5):1225-9.
71. Cantor B, Tyler T, Nelson RM, Stein GH. Oligohydramnios and transient neonatal anuria: a possible association with maternal use of prostaglandin synthetase inhibitors. J Reprod Med. 1980;24(5):220-3.
72. Kaplan BS, Restaino I, Raval DS, Gottlieb RP, Bernstein J. Renal failure in the neonate associated with *in utero* exposure to non-steroidal anti-inflammatory agents. Pediatr Nephrol. 1994;8(6):700-4.
73. Jacqz-Aigrin E, Guillonneau M, Boissinot C, Bavoux F, Hartmann JF, Blot P. Effets maternels et neonatals de l'indomethacine administree pendant la grossesse. Arch Fr Pediatr. 1993;50:307-12.
74. Pomeranz A, Korzets Z, Dolfin Z, Eliakim A, Bernheim J, Wolach B. Acute renal failure in the neonate induced by the administration of indomethacin as a tocolytic agent. Nephrol Dial Transplant. 1996;11(6):1139-41.
75. Panter KR, Hannah ME, Amankwah KS, Ohlsson A, Jefferies AL, Farine D. The effect of indomethacin tocolysis in preterm labour on perinatal outcome: a randomized placebo-controlled trial. Br J Obstet Gynecol. 1999;106:467-73.
76. Gloor JM, Muchant DG, Norling LL. Prenatal maternal indomethacin use resulting in prolonged neonatal renal insufficiency. J Perinatol. 1993;13(6):425-7.
77. Itskovitz J, Abramovi H, Brandes JM. Oligohydramnios, meconium and perinatal death concurrent with indomethacin treatment in human pregnancy. J Reprod Med. 1980;24:137-40.
78. Veersema D, De Jong PA, van Wijck JAM. Indomethacin and the fetal renal non function syndrome. Eur J Obstet Gynecol Reprod Biol. 1983;16:113-21.
79. Simeoni U, Messer J, Weisburd P, Haddad J, Willard D. Neonatal renal dysfunction and intrauterine exposure to prostaglandin synthesis inhibitors. Eur J Pediatr. 1989;148:371-3.
80. Restaino I, Kaplan BS, Kaplan P, Rosenberg HK, Witzleben C, Roberts N. Renal dysgenesis in a monozygotic twin: association with *in utero* exposure to indomethacin. Am J Med Genet. 1991;39:252-7.
81. Van der Heijden BJ, Carlus C, Narcy F, Bavoux F, Delezoide A, Gubler M. Persistent anuria, neonatal death and renal microcystic lesions after prenatal exposure to indomethacin. Am J Obstet Gynecol. 1994;171(3):617-23.
82. Bernstein J, Werner AL, Verani R. Nonsteroidal anti-inflammatory drug fetal nephrotoxicity. Pediatr Dev Pathol. 1998;1:153-6.
83. Gouyon JB, Petion AM, Sandre D, Sgro C, Bavoux F. Neonatal kidney insufficiency and intrauterine exposure to ketoprofen. Arch Fr Pediatr. 1991;48(5):347-8.
84. Alessandri JL, Abossolo T, Reynaud I, Montbrun A, Sommer JC, Tilmont P. Non-steroidal anti-inflammatory agents and pregnancy. A study of renal and digestive toxicity of niflumic acid in the perinatal period. J Gynecol Obstet Biol Reprod (Paris). 1994;23(7):813-8.
85. Fieni S, Gramellini D, Vadora E. Oligohydramnios and fetal renal sonographic appearances related to prostaglandin synthetase inhibitors. Fetal Diagn Ther. 2004;19:224-7.
86. Phadke V, Bhardwaj S, Sahoo B, Kanhere S. Maternal ingestion of diclofenac leading to renal failure in newborns. Pediatr Nephrol. 2012;27:1033-6.
87. Voyer LE, Drut R, Méndez JH. Fetal renal maldevelopment with oligohydramnios following maternal use of piroxicam. Pediatr Nephrol. 1994;8(5):592-4.
88. Koklu E, Gurgoze M, Akgun H, Ozturk MA, Poyrazoglu MH. Renal tubular dysgenesis with atypical histology and *in utero* exposure to naproxen sodium. Ann Trop Paediatr. 2006;26(3):241-5.
89. Landau D, Shelef I, Polacheck H, Marks K, Holcberg G. Perinatal vasoconstrictive renal insufficiency associated with maternal nimesulide use. Am J Perinatol. 1999;16(9):441-4.
90. Benini D, Fanos V, Cuzzolin L, Tatò L. *In utero* exposure to nonsteroidal antiinflammatory drugs: neonatal renal failure. Pediatr Nephrol. 2004;19:232-4.
91. Peruzzi L, Gianoglio B, Porcellini MG, Coppo R. Neonatal end-stage renal failure associated with maternal ingestion of cyclo-oxygenase-type 1 selective inhibitor nimesulide as tocolytic. Lancet. 1999;354(9190):1615.
92. Balasubramaniam J. Nimesulide and neonatal renal failure. Lancet. 2000;355(9203):575.
93. Magnani C, Moretti S, Ammenti A. Neonatal chronic renal failure associated with maternal ingestion of nimesulide as analgesic. Eur J Obstet Gynecol Reprod Biol. 2004;116(2):244-5.
94. Ali US, Khubchandani S, Andankar P, Parekhji S, Dubhalish V, Padhye B. Renal tubular dysgenesis associated with *in utero* exposure to nimesulide. Pediatr Nephrol. 2006;21:274-6.
95. Ng PC, So KW, Fok TF, Yam MC, Wong MY, Wong W. Comparing sulindac with indomethacin for closure of ductus arteriosus in preterm infants. J Pediatr Child Health. 1987;33(4):324-8.
96. Sakhalkar VS, Merchant RH. Therapy of symptomatic patent ductus arteriosus in preterms using mefenamic acid and indomethacin. Indian Pediatr. 1992;29:313-8.
97. Van Overmeire B, Brus F, Van Acker KJ, van der Auwera JC, Schasfoort M, Elzenga NJ, Okken A. Aspirin versus indomethacin treatment of patent ductus arteriosus in preterm infants with respiratory distress syndrome. Pediatr Res. 1995;38(6):886-91.
98. Shaffer CL, Gal P, Ransom JL, Carlos RQ, Smith MS, Davey AM, Dimaguila MA, Brown YL, Schall SA. Effect of age and birth weight on indomethacin pharmacodynamics in neonates treated for patent ductus arteriosus. Crit Care Med. 2002;30:343-8.
99. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2010;4:CD003481.
100. Mosca F, Bray M, Lattanzio M, Fumagalli M, Tosetto C. Comparative evaluation of the effcts of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus. J Pediatr. 1997;131: 549-54.

101. Pezzati M, Vangi V, Biagiotti R, Bertini G, Cianciulli D, Rubaltelli FF. Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus. J Pediatr. 1999;135:733-8.
102. Cherif A, Khrouf N, Jabnoun S, Mokrani C, Amara MB, Guellouze N, Kacem S. Randomized pilot study comparing oral ibuprofen with intravenous ibuprofen in very low birth weight infants with patent ductus arteriosus. Pediatrics. 2008;122(6):e1256-61.
103. Chotigeat U, Jirapapa K, Layangkool T. A comparison of oral ibuprofen and intravenous indomethacin for closure of patent ductus arteriosus in preterm infants. J Med Assoc Thai. 2003;86(Suppl 3):S563-9.
104. Katakam LI, Cotten CM, Goldberg RN, Dang CN, Smith PB. Safety and effectiveness of indomethacin versus ibuprofen for treatment of patent ductus arteriosus. Am J Perinatol. 2010;27:425-9.
105. Fanos V, Benini D, Verlato G, Errico G, Cuzzolin L. Efficacy and renal tolerability of ibuprofen vs indomethacin in preterm infants with patent ductus arteriosus. Fundam Clin Pharmacol. 2005;19:187-93.
106. Van Overmeire B, Allegaert K, Casaer A, Debauche C, Decaluwè W, Jespers A, Weyler J, Harrewijn I, Langhendries JP. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blid, placebo-controlled trial. Lancet. 2004;364:1945-9.
107. Aranda JV, Clyman R, Cox B, Van Overmeire B, Wozniak P, Sosenko I, Carlo WA, Ward RM, Shalwitz R, Baggs G, Seth A, Darko L. A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysinefor the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants. Am J Perinatol. 2009;26:235-45.
108. Gournay V, Roze JC, Kuster A, Daoud P, Cambonie G, Hascoet JM, Chamboux C, Blanc T, Fichtner C, Savagner C, Gouyon JB, Flurin V, Thiriez G. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2004;364:1939-44.
109. Antonucci R, Cuzzolin L, Arceri A, Dessì A, Fanos V. Changes in urinary PGE2 after ibuprofen treatment in preterm infants with patent ductus arteriosus. Eur J Clin Pharmacol. 2009;65:223-30.
110. Vieux R, Desandes R, Boubred F, Semama D, Guillemin F, Buchweiller MC, Fresson J, Hascoet JM. Ibuprofen in very preterm infants impairs renal function for the first month of life. Pediatr Nephrol. 2010;25:267-74.
111. Bagnoli F, Rossetti A, Messina G, Mori A, Casucci M, Tomasini B. Treatment of patent ductus arteriosus (PDA) using ibuprofen: renal side-effects in VLBW and ELBW newborns. J Matern Fetal Neonat Med. 2013;26(4):423-9.