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NSAID-Induced Nephrotoxicity from the Fetus to the Child

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Contents

Abstract

In this review we report data available from the literature on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and the development of nephrotoxicity in the fetus, neonates and children. Up to the present day, several cases of severe and sometimes irreversible renal insufficiency have been described in neonates exposed to indomethacin prenatally or in the first days of life for treatment of patent ductus arteriosus (PDA). Until now, very few studies have been carried out on alternative treatments for PDA in preterm infants; ibuprofen has been shown to be as effective as indomethacin in closing the ductus in this patient group without affecting renal function. In children, NSAID-induced renal failure is a rare event and is usually reversible after discontinuation of the drug. However, caution should be taken when NSAIDs are administered to individuals with preexisting renal problems or with other potentially nephrotoxic drugs. In these situations, new approaches such as cyclo-oxygenase-2 selective inhibitors or prostanoid receptor selective antagonists could lead to alternative therapies for use in paediatrics.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used drugs in medicine and their use has dramatically increased in recent years.[1] Current studies indicate that NSAIDs account for 7% of reported cases of acute renal failure and 35% of renal failure related to drug therapy in the general population.[2] In adults, NSAID-induced renal impairment occurs primarily in patients with preexisting renal disease or other conditions associated with low intravascular volume or low cardiac output such as congestive heart failure, nephrotic syndrome, hypertension, sepsis or diabetes mellitus.[3,4] Under these conditions, the balance between the vasoconstrictors and the vasodilators is tipped in favour of the vasoconstrictors. In fact renal blood flow is regulated by processes involving prosta-

glandins, vasodilating substances and protective agents for renal blood flow and glomerular filtration rate, which work in opposition to vasoconstrictors such as catecholamines, angiotensin II, vasopressin and endothelin.[5] Inhibition of prostaglandins by NSAIDs may provoke renal damage which may result in acute renal failure (with or without oliguria), chronic renal failure, clinically relevant proteinuria, acute interstitial nephritis, fluid metabolism alterations or hyperkalaemia.[6] The nephrotoxic effects of NSAIDs are related to inhibition of the cyclo-oxygenase (COX) enzyme, of which 2 isoforms are known. COX-1 is a constitutional enzyme present in most tissues, including the kidneys. Although COX-2 has also recently been identified in the kidneys (see section 1), selective inhibition of COX-2 enhances both the efficacy and safety of NSAIDs.[7]

In this review we report and comment on available literature regarding the use of NSAIDs and the development of nephrotoxicity in the fetus, neonates and children. For this purpose, a MEDLINE search was performed from 1978 to the present day to identify pertinent English language literature including clinical trials, case reports and review articles; additional literature was obtained from the reference lists of articles identified through the search and from a search from 1986 to the present day of Reactions Weekly™ (Adis International), a newsletter which summarises information on adverse drug experiences reported in the world's biomedical literature.

1. Prostaglandins, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Renal Function

Prostaglandins act as local mediators that regulate a variety of renal functions, such as sodium and water homeostasis. After oxygenation of arachidonic acid by COX to prostaglandin H_2 (PGH_2), metabolism by secondary enzymes results in 5 primary bioactive prostanoids: PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane A_2 (TXA_2).[8] These lipid mediators are actively synthesised within the kidney and interact with a family of distinct receptors that are expressed in highly restricted regions along the nephron and exert important regulatory effects on renal function.[9]

In humans, the importance of renal prostaglandins becomes evident during treatment with NSAIDs. These drugs inhibit the COX enzyme and block prostaglandin synthesis, thus precipitating renal failure in susceptible individuals[10] and causing severe, albeit rare, renal complications in infants exposed to NSAIDs *in utero*.[11]

Two isoforms of COX, designated COX-1 and COX-2, have been identified. COX-1 is constitutively expressed in several tissues and is thought to participate in 'house-keeping' functions. COX-2 is undetectable in most tissues but is induced by a variety of stimuli and is associated with inflammation.[7] Constitutive expression of COX-2 has recently been reported in certain tissues including the kidneys;[12] in particular, the renal medulla displays one of the highest rates of COX-2 expression, while COX-1 appears to be predominantly expressed in collecting ducts.[13] Kömhoff et al.[14] demonstrated a basal and distinct expression of both COX isoforms in normal human kidney, suggesting a contribution of COX-2 to the regulation of glomerular haemodynamics (via production of PGH_2, subsequently metabolised to TXA_2) and the involvement of COX-1 in human nephrogenesis via production of PGE_2. Compared with COX-1, the glomerular expression of COX-2 occurs much later in the developmental process of the glomerulus in the human fetus and is detectable after vascularisation of glomeruli. Slater et al.[15] studied the expression of the 2 COX isoforms in human fetal membranes throughout pregnancy and reported that an up-regulation of COX-2, rather than of COX-1, mediates increased prostaglandin synthesis within the fetal membranes before and during term and preterm labour. These considerations have led some investigators to use selective COX-2 inhibitors in the management of preterm labour; nimesulide, which may be free of adverse effects caused by COX-1 inhibition, has been suggested as a potential tocolytic agent.[16] Other authors have hypothesised that COX-2 selective inhibitors might be

better alternatives for the fetus than nonselective COX inhibitors with regards to adverse effects on the ductus arteriosus, even though in the ductus arteriosus COX-1 and COX-2 expression showed some differences among animal species, for example, in pigs,[17] baboons[18] and lambs.[19] Since basal expression of both COX isoforms has been demonstrated in normal human kidney, we agree with other authors[14] that the development of a completely renal-sparing NSAID is unlikely.

Since NSAIDs affect all prostanoids, which often have opposing actions among themselves, another new approach may be the development of prostanoid receptor-selective antagonists providing novel physiological and therapeutic tools. The role of PGD_2 and $PGF_{2\alpha}$ and their respective prostaglandin D_2 and prostaglandin $F_{2\alpha}$ (FP) receptors in regulating renal function is poorly defined, even though some authors have suggested that FP receptors may modulate glomerular contraction.[20] Four prostaglandin E_2 (EP) receptor subtypes have been cloned and characterised.[21] The renal EP_1 receptor may contribute to the natriuretic and diuretic actions of PGE_2 and may be present in glomerular mesangial cells, where it could have a role as a vasoconstrictor.[22] EP_2 receptors exhibit only low levels of expression in the kidney, but may have an important role in protecting systemic blood pressure, perhaps via its vasodilator effect.[21] Relatively high levels of EP_3 receptor expression have been observed in the kidney[23] and, as observed with EP_1 receptors, it may contribute to the natriuretic actions of PGE_2. Important vasodilator effects of EP_4 receptor activation have been described in renal venous and arterial beds,[24] and a particular role for this receptor in regulating the perinatal closure of the pulmonary ductus arteriosus has been suggested.[25] PGI_2, through prostaglandin I_2 receptors, has been shown to be important in the glomerular microvasculature[26] as well as in regulating renin release.[27] Glomerular localisation of prostaglandin thromboxane A_2 (TP) receptors corresponds to the vasoconstrictor effects of TXA_2 on glomerular capillaries and the TXA_2-induced decrease in glomerular filtration rate.[28] Together, all of these receptors protect the kidney from excessive functional changes during periods of physiological stress, and loss of the combined effects of these receptors may contribute to the adverse effects seen with NSAID administration; thus selective antagonists for these receptors may provide new therapeutic approaches for the management of NSAID-induced adverse renal effects.[20]

2. Nephrotoxicity

2.1 Prenatal Exposure to NSAIDs

NSAIDs, like all drugs, should be used with care during pregnancy. Yet NSAIDs, particularly indomethacin, have been used for many years as tocolytic agents to prevent premature uterine contractions[29] and to treat polyhydramnios.[30] However, the use of these drugs has been associated with constriction of the fetal ductus arteriosus with serious consequences. The proportion of fetuses developing ductal constriction increases with gestational age at the same time of NSAID-exposure with 100% experiencing constriction at >34 weeks' gestation;[31] however this is usually reversible when the drug is stopped.

The underlying mechanisms leading to renal dysfunction in the fetus are probably the same as those in postnatal and adult life. The major role of prostaglandins synthesised by the fetal kidney seems to be maintenance of adequate renal perfusion, and fetuses with suboptimal circulation, as in the case of twin pregnancies, have high circulating levels of angiotensin II and are more susceptible to the vasoconstricting effects of prostaglandin inhibition.[32]

The occurrence of renal complications seems to be rare considering the large number of pregnant women treated with indomethacin or other prostaglandin inhibitors;[33-36] however, up to the present day several cases of severe and sometimes irreversible renal insufficiency have been described in human neonates exposed to indomethacin during fetal life.

The adverse effects associated with NSAIDs after prenatal exposure are presented in table I. In a

Table I. Summary of adverse effects occurring after prenatal exposure to nonsteroidal anti-inflammatory drugs

Reference	Study design	No. of individuals exposed to active drug	Drug	Adverse effects (% of patients)
Itskovitz et al.[37]	CR	3	IND	Oligohydramnios, fatal anuria
Jacqz-Aigrin et al.[38]	NC	23	IND	Renal failure (22)
Kaplan et al.[11]	CR	6	IND, IBU	Renal failure[a]
Norton et al.[39]	CC	57	IND	Intracranial haemorrhage (28), necrotising enterocolitis (29), PDA (62), oliguria, ↑ serum creatinine levels (NR)
Panter et al.[40]	RCT	19	IND *vs* PL	Oliguria (32)
Pomeranz et al.[41]	CR	2	IND	Renal failure, metabolic acidosis, PDA
Restaino et al.[42]	CR	1	IND	Fatal anuria
Simeoni et al.[43]	CR	1	IND	Fatal anuria
Souter et al.[44]	CC	39	IND	Periventricular haemorrhage (27), PDA (40), ↑ serum creatinine levels (NR)
Van der Heijden et al.[45]	CR	6	IND	Fatal anuria
Veersema et al.[46]	CR	1	IND	Fatal anuria

a Occurring with IND and IBU.

CC = case-control; **CR** = case report; **IBU** = ibuprofen; **IND** = indomethacin; **NC** = noncomparative; **NR** = not reported; **PDA** = patent ductus arteriosus; **PL** = placebo; **RCT** = randomised controlled trial.

case-control study, 57 babies exposed to indomethacin prenatally, born at or before 30 weeks' gestation, had an increased incidence of intracranial haemorrhage, necrotising enterocolitis and patent ductus arteriosus (PDA);[39] a reduction in urine output and a moderate increase in serum creatinine levels were also observed during the first 3 days of life in these neonates.[39] A similar study reported that babies born at less than 31 weeks' gestation had an increased incidence of periventricular haemorrhage, PDA and renal function impairment when they were delivered within 48 hours of their last *in utero* exposure to indomethacin.[44]

Itskovitz et al.[37] described the occurrence of oligohydramnios, neonatal anuria and perinatal death in 3 neonates after 1 week's exposure to indomethacin *in utero*. Other authors[38,42,43,46] observed 3 cases of fatal anuria in fetuses after some weeks of indomethacin therapy. Five of 23 neonates born after prenatal exposure to indomethacin developed transient renal insufficiency.[38] More recently, Van der Heijden et al.[45] reported that 6 neonates exposed *in utero* to indomethacin for at least 5 weeks died of anuria. In another report,[11] renal failure was associated with prolonged *in utero* exposure to indomethacin in 4 neonates and to ibuprofen in a set of twins. Pomeranz et al.[41] described transient acute renal failure in a pair of twins delivered at 34 weeks' whose mother had received indomethacin in the last 2 weeks for premature contractions. Finally, a significantly higher incidence of oliguria was observed in the first 24 hours of life in babies born at less than 30 weeks of gestation whose mothers were exposed to indomethacin for preterm labour compared with those exposed to placebo *in utero*.[40]

2.2 NSAID Exposure in the Neonatal Period

PDA normally undergoes spontaneous physiological closure by the third day of life. In preterm infants, however, ductal closure is inversely related to gestational age, and in neonates of less than 30 weeks' gestation or less than 1000g birth weight the incidence of nonclosure may be in excess of 75%.[47] Left to right shunting through a PDA causes several undesirable pulmonary, haemodynamic, renal and gastrointestinal effects and increases the risk of intraventricular haemorrhage and bronchopulmonary dysplasia. Therefore treatment of PDA with NSAIDs, through the inhibition of prostaglandin synthesis, is indicated before this left to right shunting occurs.[48,49] However, this

type of therapy may itself cause adverse effects such as nephrotoxicity due either to the immature neonatal kidney or to the mechanism of action of the drugs; in fact, very little is known about the expression of COX isoenzymes in neonatal tissue.[50] Adverse effects associated with NSAID use during the neonatal period are presented in table II.

For many years indomethacin has been the drug of choice in the treatment[47,59,63-65] and prophylaxis[55,66-68] of PDA in premature neonates. However, adverse effects such as transient or permanent alterations in renal function,[52-54] necrotising enterocolitis,[39] gastrointestinal haemorrhage[53,59] and impairment of cerebral blood flow[69] have been frequently observed even at low doses (0.2 mg/kg). Reduction of urinary volume and glomerular filtrate are usually reversible within 48 hours after discontinuation of therapy, although oliguria may persist for 2 weeks.[51] Strategies to minimise the adverse renal effects associated with indomethacin, such as the administration of furosemide or low doses of dopamine or the use of prolonged low doses of indomethacin, have not been successful.[70-73] Other NSAIDs have also been used to treat PDA in preterm infants but were associated with adverse effects, as in the case of sulindac[57] and mefenamic acid,[74,75] or were less effective than indomethacin at closing the duct, as was shown for aspirin (acetylsalicylic acid).[61]

Ibuprofen has been shown to close the ductus arteriosus in animals.[76] However, in contrast to indomethacin, ibuprofen does not seem to affect cerebral blood flow and cerebral metabolic rate[77,78] or intestinal and renal haemodynamics.[79] Ibuprofen has also been shown to protect neurological function following oxidative stress in animal models.[80]

Very few studies have been carried out on ibuprofen for the treatment of PDA in preterm infants. It was concluded from studies in neonates that ibuprofen, compared with indomethacin, is effective at closing the duct and is associated with fewer cerebral[56,58] and renal adverse effects.[81] Recently its prophylactic use, although not yet uniformly accepted, has been advocated. In a phase I trial Varvarigou et al.[62] observed that, despite the lack of clinical efficacy of a single dose, administration of 3 doses of ibuprofen lysine (10 mg/kg intravenously) to 34 premature neonates within 3 hours of birth reduced the incidence of PDA and the severity of the respiratory status without affecting renal func-

Table II. Summary of adverse effects of nonsteroidal anti-inflammatory drugs after exposure during the neonatal period

Reference	Study design	Total no. of individuals studied	Drug	Adverse effect (% of patients)
Aranda et al.[51]	NC	21	IBU	Oliguria
Betkerur et al.[52]	RCT	21	IND *vs* PL	Oliguria (45)
Kuo[53]	CR	3	IND	Gastrointestinal haemorrhage, renal failure
Lin et al.[54]	NC	10	IND	Renal failure (NR)
Ment et al.[55]	RCT	431	IND *vs* PL	None
Mosca et al.[56]	RCT	16	IND *vs* IBU	↓ cerebral blood flow in IND patients (50)
Ng et al.[57]	RCT	16	IND *vs* SUL	Oliguria, ↑ serum creatinine in IND recipients
Patel et al.[58]	CS[a]	33	IND *vs* IBU	↓ cerebral blood flow in IND recipients
Rennie et al.[59]	RCT	50	IND *vs* PL	Gastrointestinal haemorrhage (14), ↑ serum creatinine levels
Van Bel et al.[60]	NC	15	IND	Renal failure
Van Overmeire et al.[50]	RCT	40	IND *vs* IBU	Oliguria (40 for IND; 5 for IBU), ↑ serum creatinine levels
Van Overmeire et al.[61]	RCT	75	IND *vs* ASP	Oliguria in IND recipients (50)
Varvarigou et al.[62]	RCT	34	IBU *vs* PL	None

a Trial design not stated.

ASP = aspirin (acetylsalicylic acid); **CR** = case report; **CS** = comparative study; **IBU** = ibuprofen; **IND** = indomethacin; **NC** = noncomparative; **NR** = not reported; **PL** = placebo; **RCT** = randomised controlled trial; **SUL** = sulindac.

tion. In a prospective randomised study[50] comparing the effectiveness and adverse effects of ibuprofen and indomethacin in the treatment of PDA in preterm infants with respiratory distress syndrome (RDS), 3 doses of ibuprofen given on the third day of life (10 mg/kg followed by 5 mg/kg after 24 and 48 hours) was as effective as indomethacin in closing the ductus without decreasing urinary output or increasing serum creatinine levels. This was also observed by other authors.[82]

2.3 NSAID-Induced Nephrotoxicity in Children

Renal failure has been reported to be a rare event among children exposed to NSAIDs,[83,84] and is usually reversible after discontinuation of the drug. Moreover, it is unclear how adult experiences apply to children who may be more or less susceptible to renal injury by NSAIDs. Children may be at lower risk because they are less likely than adults to have other factors predisposing to acute renal disorders; conversely, they may be at greater risk because some degree of dehydration is likely to accompany fever, the most common indication for the use of NSAIDs in children.[85]

A number of reports, mainly case reports, have linked NSAID use to renal complications in children. However, case reports do not provide estimates of the rate at which renal failure occurs, and observational nonrandomised studies cannot provide valid estimates of risk when the choice of treatment is influenced by the severity of illness.[86,87] Finally, randomised clinical trials designed to test the efficacy of NSAIDs in children have typically been too small to detect even modest increases in the risk of mild renal impairment.

Adverse effects associated with NSAID use in children are presented in table III. Three reports have described renal failure in children younger than 15 years after short term treatment with ibuprofen at therapeutic doses: a case of acute renal failure with oedema in a 10-year-old,[96] episodes of acute flank pain and non-oliguric renal failure in adolescent girls,[83] and a case of interstitial nephritis documented by renal biopsy.[84] In another report 4 patients were admitted to the Children's Hospital of Philadelphia, US, between May 1996 and June 1997 with a diagnosis of acute non-oliguric renal failure following ingestion of unspecified NSAIDs.[94] Recently, a case of irreversible renal failure was observed in an adolescent treated with ketorolac.[95]

Table III. Summary of adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) after administration to children

Reference	Study design	Total no. of individuals studied	Drug	Adverse effect
Al-Harbi et al.[88]	CR	1	IBU	Renal failure, metabolic acidosis, hypocalcaemia
Kelley et al.[89]	RCT	119	IBU *vs* PAR *vs* PL	↑ BUN with IBU and PAR
Kim et al.[90]	CR	1	IBU	Acute renal failure
Kovesi et al.[91]a	CR	4	IBU	Acute renal failure
Lesko & Mitchell[92]	RCT	83 915	IBU *vs* PAR	None had acute renal failure
Lesko & Mitchell[85]	RCT	83 915	IBU *vs* PAR	Slight ↑ BUN with IBU and PAR, ↑ serum creatinine
McIntire et al.[83]	CR	2	IBU, FBP	Acute renal failure, acute flank pain
Moghal et al.a[93]	CR	3	IBU	Acute renal failure
Schaller & Kaplan[94]	CR	4	NSAIDb	Acute renal failure
Simckes et al.[95]	CR	1	KET	Irreversible renal failure
Van Biljou[96]	CR	1	IBU	Acute renal failure
Wattad et al.[84]	CR	1	IBU	Interstitial nephritis

a Children had pre-existing renal impairment[93] or were receiving concomitant aminoglycosides.[91]

b Specific NSAIDs not reported.

BUN = blood urea nitrogen; **CR** = case report; **FBP** = flurbiprofen; **IBU** = ibuprofen; **KET** = ketorolac; **PAR** = paracetamol (acetaminophen); **PL** = placebo; **RCT** = randomised controlled trial.

Renal failure has also been reported in 2 healthy 2-year-old children after an overdose of ibuprofen.[88,90]

In a clinical trial involving 119 febrile children, increases in blood urea nitrogen (BUN), although not statistically significant, were observed after administration of a single dose of ibuprofen (5 to 10 mg/kg), but no increase in creatinine levels was observed either for ibuprofen or paracetamol (acetaminophen) recipients.[89] In a randomised trial involving 83 915 children (of whom 55 785 were treated with ibuprofen for fever), no renal impairment was observed. The authors compared short term ibuprofen use with paracetamol and did not find significant differences between the 2 treatments in the risk of renal failure.[92] In another paper concerning the same population, [85] the same authors found that the risk of less severe renal impairment in the 795 of 83 915 patients who required hospitalisation (1%), as reflected by BUN and serum creatinine values, was small and not significantly greater for ibuprofen than it was with paracetamol use. The prevalence of BUN levels greater than 18 mg/dl and creatinine levels higher than 0.7 mg/dl were slightly higher in the 108 children with a concomitant diagnosis of dehydration, both for ibuprofen and paracetamol.

Finally, caution should be taken when NSAIDs are administered to individuals with pre-existing renal problems or in association with other potentially nephrotoxic drugs. Moghal et al.[93] reported 3 cases of renal impairment of varying degrees in children treated with ibuprofen for fever (1 child had a pre-existing renal condition), and transient renal failure was reported in children with cystic fibrosis receiving aminoglycosides and ibuprofen simultaneously.[91]

3. Conclusions

Drug-induced renal injury remains an important clinical problem in paediatric medicine, particularly in neonates, in whom the functionally immature kidney may exert a significant effect on the disposition of the drugs.[97]

Although the overall occurrence of renal failure due to NSAID administration appears to be rare among children,[83,84] severe renal complications during fetal life and in neonates have been reported.[11,52,54,60] However, relatively little information is available about the use of NSAIDs in pregnancy and in paediatrics. However, information on the adverse renal effects affecting the fetus, neonates and children after NSAID use is sparse. In recent years, the use of new COX-2-selective inhibitors with fewer adverse renal effects has been advocated;[98] moreover, the discovery of prostanoid receptors could provide novel targets for modulating renal function without producing adverse effects.[20] These new approaches may lead to alternative therapies in paediatrics, although further functional and biochemical studies are needed to elucidate the roles of prostaglandin receptors and COX isoforms in human nephrogenesis and paediatric renal physiology.

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