European Review for Medical and Pharmacological Sciences 2011; 15: 1461-1472

Acute nephrotoxicity of NSAID from the foetus to the adult

M. MUSU[1], G. FINCO[1], R. ANTONUCCI[2], E. POLATI[3], D. SANNA[1], M. EVANGELISTA[4], D. RIBUFFO[5], V. SCHWEIGER[3], V. FANOS[2]

[1]Department of Medicine "M. Aresu", University of Cagliari, Cagliari (Italy)
[2]Neonatal Intensive Care Unit, University of Cagliari, Cagliari (Italy)
[3]Department of Anesthesiology and Intensive Care, University of Verona, Verona (Italy)
[4]Department of Emergency, Catholic University of the Sacred Heart, Rome (Italy)
[5]Department of Surgery, University of Cagliari, Cagliari (Italy)

Abstract. – NSAIDs are generally considered to be safe and well tolerated, but, even with the advent of selective COX-2 inhibitors, nephrotoxicity remains a concern. An impaired renal perfusion caused by the inhibition of prostaglandin synthesis is claimed like the more frequent cause of an acute renal failure due to NSAIDs, while a chronic interstitial nephritis or an analgesic nephropathy are believed the causes of a chronic renal failure. The real incidence of renal side effects of NSAIDs is still unclear and it differs between the age of the patients and the reports present in the literature. The occurrence of renal side effects following prenatal exposure to NSAIDs seems to be rare considering the large number of pregnant woman treated with indomethacin or other prostaglandin inhibitors. NSAID-related nephrotoxicity remains an important clinical problem in the newborns, in whom the functionally immature kidney may exert a significant effect on the disposition of the drugs. Instead, nephrotoxicity is a rare event in children and the risk is lower than adults. In healthy adult patients the incidence of renal adverse effects is very low, less than 1%. The risk increased with age. The elderly are at higher risk, and it is correlated at the presence of pretreatment renal disease, hypovolemia due to use of diuretics, diabetes, congestive heart failure or alteration of NSAID pharmacokinetics.

Key Words:

NSAIDs, Nephrotoxicity, Renal failure, Newborn, Child, Adult.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used drugs in medicine and their use has dramatically increased in recent years. NSAIDs are the most commonly used class of medications for the treatment of pain and inflammation, with an estimated usage of over 30 million people per day.

NSAIDs often are administered during pregnancy and in newborns too. Particularly indomethacin, have been used for many years as tocolytic agents to prevent premature uterine contractions and to treat polyhydramnios. In very low birth weight (VLBW) neonates, low-dose prophylactic indomethacin significantly lowers the incidence and severity of intraventricular hemorrhage (IVH). For many years, indomethacin has been the drug of choice for the treatment[1] and prophylaxis of patent ductus arteriosus (PDA) in preterm infants.

NSAIDs are generally considered to be safe and well tolerated, but current studies indicate that these pharmacological agents account for 7% of reported cases of acute renal failure and 35% of drug-induced acute renal failure in the general population[2]. This review discusses the available literature data concerning NSAID-related nephrotoxicity, in the foetus, newborn, child, and adult, with special emphasis on its clinical aspects.

Pathophysiology of NSAID-induced Nephrotoxicity

Prostaglandins are biologically active lipids derived from the 20-carbon essential fatty acids, acting as modulators and mediators in a large spectrum of physiological processes and pathophysiological conditions[3]. In addition to their role in inflammation, prostaglandins regulate a

Corresponding Author: Gabriele Finco, MD; e-mail: gabriele.finco@gmail.com

variety of renal functions such as vascular tone, salt and water balance, and renin release[4].

COX-1 is constitutively expressed in several tissues and is thought to participate in "housekeeping" functions. In the kidney, it has been localized to mesangial cells, arteriolar smooth muscle and endothelial cells, parietal epithelial cells of Bowman's capsule, and cortical and medullary collecting ducts. This COX isoform controls homeostatic functions such as regulating renal blood flow[5].

COX-2 is undetectable in most tissues but is induced by a variety of stimuli and is associated with inflammation. Constitutive expression of COX-2 has been reported in certain tissues including the kidneys[5]. Indeed, COX-2 mRNA and immunoreactive protein are present at detectable levels in normal adult mammalian kidney, namely in macula densa (MD) cells and in scattered cells in the cortical thick ascending limb cells immediately adjacent to the MD[6]. In human kidney, COX-2 expression has been reported to be present in podocytes and arteriolar smooth muscle cells[7]. COX-2 expression is also abundant in the lipid-laden medullary interstitial cells in the inner medulla and papilla. Some investigators have reported that COX-2 may also be expressed in inner medullary collecting duct cells or intercalated cells in the renal cortex[8]. Nevertheless, constitutively expressed COX-1 is clearly the most abundant isoform in the collecting duct, so the physiological significance of COX-2 coexpression in these cells remains unclear. Moreover, a recent report has suggested that, in human kidney, there is significant COX-2 expression in the medullary vasa recta[7].

COX-2 seems to be involved in the regulation of glomerular haemodynamics, and has been demonstrated to play a major role in nephrogenesis[8].

Slater et al[9] studied the expression of the 2 COX isoforms in human foetal membranes throughout pregnancy and reported that an upregulation of COX-2, rather than COX-1, mediates increased prostaglandin synthesis within the foetal 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[10].

Prostaglandins 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[11].

In humans, the importance of renal prostaglandins becomes evident during treatment with NSAIDs, which inhibit the COX enzyme and block prostaglandin synthesis. There is a reasonably good correlation between the potency of these drugs as cyclooxygenase inhibitors and their anti-inflammatory activity[12]. NSAID treatment may precipitate renal failure in susceptible individuals and cause severe, albeit rare, complications in infants exposed to NSAIDs in utero[13]. Four PGE2 receptor subtypes (EP1, EP2, EP3, and EP4) have been cloned and characterised and present different properties. For example, the renal EP1 receptors may contribute to the natriuretic and diuretic actions of PGE2 and may be present in glomerular mesangial cells, where it could have a role as vasoconstrictor[14]. EP2 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[15]. All prostanoid receptors act in concert as physiological buffers to protect the kidney from excessive functional changes during periods of physiological stress, and the loss of the combined effects of these receptors may contribute to the adverse effects seen with NSAID administration. Therefore, selective prostanoid receptor antagonists may provide new therapeutic approaches for the management of NSAID-induced adverse renal effects[16].

Evidences and Information Sources

Effects of NSAIDs on renal function were examined in published literature indexed by PubMed from 1980 to August 2010, in order to identify English language literature concerning acute renal failure in foetus, newborn, child and adult under NSAID's therapy. The available literature data were reviewed with special emphasis on their clinical aspects.

Using electronic database, we looked for suitable multicentric and prospective randomized controlled trials (RCT), comparative studies, reviews, case series, case reports, on humans and animals. The terms and text words (and their combinations and truncated synonyms) were adapted as appropriate to search by combining the terms NSAIDs AND nephrotoxicity, or and renal failure, both and newborn or child or adult.

State of the Art

Nephrotoxicity During the Prenatal Period

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 and to treat polyhydramnios. However, the use of these drugs has been associated with constriction of foetal ductus arteriosus with severe consequences. The proportion of foetuses developing ductal constriction after indomethacin exposure increases with advancing of gestational age, with 100% experiencing constriction at >34 weeks' gestation[17]. However, this effect is usually reversible when the drug is stopped. The underlying mechanisms leading to renal dysfunction in the foetus are probably the same as those in postnatal and adult life.

The major adverse effects associated with NSAID prenatal exposure are oligohydramnios, fatal anuria, renal failure, intracranial haemorrhage, necrotising enterocolitis, patent ductus arteriosus (PDA), oliguria, augmentation of serum creatinine levels and metabolic acidosis.

The occurrence of renal complications following prenatal exposure to NSAIDs seems to be rare considering the large number of pregnant women treated with indomethacin or other prostaglandin inhibitors[18]. 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, as discussed below. In a case-control study, 57 babies exposed prenatally to indomethacin, born at or before 30 weeks' gestation, had an increased incidence of intracranial hemorrhage, necrotising enterocolitis and PDA[19]. A reduction in urine output and a moderate increase in serum creatinine levels were also observed during the first three days of life in these neonates. 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[20]. Itskovitz et al[21], described the occurrence of oligohydramnios, neonatal anuria and perinatal death in 3 neonates after 1 week's in utero exposure to indomethacin. Other Authors observed 3 cases of fatal anuria in foetuses after some weeks of indomethacin therapy[22-24]. Five of 23 neonates born after prenatal exposure to indomethacin developed transient renal insufficiency[25].

More recently, Van der Heijden et al[26] reported that 6 neonates exposed to indomethacin in utero for at least 5 weeks died of anuria. Pomeranz et al[27] described transient acute renal failure in a pair of twins delivered at 34 weeks' whose mother had received indomethacin in the last two weeks for premature contractions. Finally, a significantly higher frequency of oliguria was observed, in the first 24 hours of life, in babies born at less than 30 weeks' gestation whose mothers had been exposed to indomethacin for preterm labour, compared with babies exposed to placebo in utero[28].

A summary of renal adverse effects occurring after prenatal exposure of some NSAIDs is presented in Table I.

NSAID Exposure in Neonatal Period

Patent ductus arteriosus (PDA) is a very important pathology in the neonatal period by an epidemiologic, clinic and therapeutic point of view. Physiopathology has been extensively review very recently[29]. Treatment of PDA with NSAIDs, through the inhibition of prostaglandin synthesis, is indicated before left to right ductal shunting occurs[30] and a recent 3rd Cochrane review has been dedicated to this argument[31]. Benitz[32] very recently greatly criticised contemporary terapeutic approach.

However, during the neonatal period, this type of therapy may itself cause adverse effects such as oliguria, gastrointestinal haemorrhage, renal failure, decrease of cerebral blood flow, and increase of serum creatinine levels.

For many years, indomethacin has been the drug of choice in the treatment[1] and prophylaxis[33] of PDA in premature neonates. However, adverse effects such as transient or permanent alterations in renal function[34], necrotising enterocolitis[19], gastrointestinal haemorrhage[34], and impairment of cerebral blood flow[35] have been frequently observed even at low doses (0,2 mg/kg). Reduction of urinary volume and glomerular filtration rate are usually reversible within 48 hours after discontinuation of therapy, although oliguria may persist for 2 weeks[36]. Strategies to minimise the adverse renal effects associated with indomethacin, such as the use of prolonged low doses of this drug, or the co-administration of indomethacin and other pharmacological agents (furosemide or dopamine), have not been successful[37]. Other NSAIDs have

Table I. Summary of renal adverse effects occurring after prenatal exposure of some anti-inflammatory drugs (NSAIDs).

Author	N° of individual studied exposed to the drug	Drug	Renal adverse effect
Norton ME, et al[19]	57	Indomethacin	Oliguria, ↑ serum creatinine levels
Souter D, et al[20]	39	Indomethacin	↑ serum creatinine levels
Panter KR, et al[28]	19	Indomethacin vs Placebo	Oliguria
Itskovitz J, et al[21]	3	Indomethacin	Oligohydramnion, fatal anuria
Jacqz-Aigrin E, et al[25]	23	Indomethacin	Renal failure (in 5 subjects)
Van der Heijden BJ, et al[26]	6	Indomethacin	Fatal anuria (in all 6 subjects)
Kaplan BS, et al[13]	6	Indomethacin-Ibuprofen	Renal failure

also been used to treat PDA in preterm infants but have been shown to be associated with adverse effects, as in the case of sulindac and mefenamic acid[38] or to be less effective than indomethacin at closing the duct, as in the case of acetylsalicylic acid[39].

Relatively few studies have evaluated ibuprofen therapy in preterm infants with PDA. The results of these investigations have demonstrated that ibuprofen, compared with indomethacin, is effective at closing the duct and is associated with fewer cerebral[33] and renal adverse effects[40]. Recently its prophylactic use, although not yet uniformly accepted, has been advocated. In a phase I trial, Vargarigou et al[41], observed that the administration to 34 premature neonates of one dose of ibuprofen lysine (10 mg/kg intravenously) within 3 hours after birth, followed by 5 mg/kg per dose intravenously at 24 and 48 hours of age, reduced the incidence of PDA and the severity of the respiratory status without affecting renal function. In a prospective randomised study, Van Overmeire et al[42] compared the effectiveness and adverse effects of intravenous ibuprofen (an initial dose of 10 mg/kg followed by 5 mg/kg 24 and 48 hours later) and intravenous indomethacin (3×0.2 mg/kg at 12-hour intervals), starting on the third day of life, in the treatment of PDA in preterm infants with acute respiratory distress syndrome (ARDS). Ibuprofen was as effective as indomethacin in closing the ductus without decreasing urinary output or increasing serum creatinine levels. NSAID-related nephrotoxicity in the newborn may result from the mechanism of action of these drugs combined with renal immaturity. By blunting the effect of prostaglandins on the afferent arteriole, NSAIDs can impair glomerular filtration rate in both the foetus and the newborn.

Three different hypothesis have been advocated to explain the difference in renal side effects between indomethacin and ibuprofen: (1) one possibility is that both drugs inhibit the cyclooxygenase isozymes to different extents in the neonatal kidney; (2) the different pharmacokinetic characteristics result in different potentials to impair renal function; (3) the possibility of non-prostaglandin effects.

Very recently we described longterm effects of NSAIDs on renal function and renal volume, namely in extremly low birth weight (ELBW)[43].

NSAID-induced Nephrotoxicity in Children

Renal failure has been reported to be a rare event in children exposed to NSAIDs and is usually reversible after discontinuation of the drug[44]. Children may be at great risk of nephrotoxicity in some conditions like dehydration accompanying fever, the most common paediatric indication for NSAID treatment[45].

Adverse effects associated with NSAID use in children are renal failure, metabolic acidosis, hypocalcemia, acute flank pain and interstitial nephritis[46-49].

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[50]. In a randomised trial involving 83,915 children[51], 55,785 of whom were treated with ibuprofen for fever, no renal impairment was observed. Moreover, the risk of renal failure was not increased following short-term use of ibuprofen compared to paracetamol. Another study concerning the same population[45] showed that the risk of less severe renal impairment, in the 795 of 83,915 patients who required hospitalisation, was small and not significantly greater for ibuprofen than for paracetamol. The prevalences 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 in ibuprofen-treated subjects and paracetamol-treated subjects. Finally, caution should be taken when NSAIDs are administered to individuals with underlying renal disorders or in association with other potentially nephrotoxic drugs. Moghal et al[52] reported renal impairment of varying degrees following ibuprofen treatment in 3 children with intravascular volume depletion and/or pre-existing renal problems. On the other hand, transient renal failure was reported[53] in children with cystic fibrosis receiving aminoglycosides and ibuprofen simultaneously.

A summary of renal adverse effects of NSAIDs after administration in children is presented in Table II.

NSAID-induced Nephrotoxicity in Adults

In addition to various side effects, both acute and chronic renal failures have been observed in patients treated with non-specific and specific COX-2 inhibitors[54,55]. NSAID-induced nephrotoxicity includes acute renal failure due to haemodynamic changes in the kidney, tubulointerstitial nephritis, glomerular lesions, reduced sodium and water excretion, hyperkaliemia and hypertension[54,56,57].

Renal adverse effects elicited by NSAIDs are dose-dependent[58]. In healthy adult patients the incidence of renal adverse effects is very low (<1%). However, the elderly are at higher risk. Indeed, the latter may present age-related decline in glomerular filtration rate, hypovolemia due to use of loop diuretics, diabetes, congestive heart

Table II. Summary of renal adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) in children.

Author	N° of individual studied	Drug	Renal adverse effect
Van Biljoun[46]	1	Ibuprofen	ARF + Oedema
McIntire et al[44]	2	Ibuprofen, flurbiprofen	Non oliguric ARF + acute flank pain
Kim et al[49]	1	Ibuprofen	ARF
Kelly et al[50]	3	Ibuprofen	Renal impairment of varyng degrees
Kovesi et al[53]	4 (Cystic fibrosis)	Ibuprofen	ARF
Simckes et al[48]	1 (Sickle cell disease)	Ketoprofen	Irreversible ARF
Becker-Cohen R and Frishberg Y[85]	1 (Juvenile rheumatoid arthritis)	Naproxen	Intestitial nephritis-ARF
Ulinski et al[86]	7	Ketoprofene, Ibuprofen	ARF
Schaller S, Kaplan BS[47]	4	Unspecified NSAID	Non oliguric ARF
Krause et al[87]	7	Unspecified NSAID	ARF + acute flank pain + abdominal pain + vomiting
Fletcher et al[88]	3	Vioxx	ARF

failure (CHF), cirrhosis or nephrosis[59], morbid conditions leading to worsening of renal function or alteration of NSAID pharmacokinetics (higher free drug levels, higher concentration of drug, slowed hepatic metabolism of drug)[57].

Moreover, the elderly frequently presents hypertension treated with antihypertensive drugs including β-blockers, ACE–inhibitors or diuretics. NSAIDs alter the effect of these antihypertensive drugs, eliciting an impairment of controlled hypertension, particularly in patients treated with ACE-inhibitors[60].

Furthermore, evidence has been provided that both diclofenac and indomethacin induce significant decreases in glomerular filtration rate (GFR), urine flow, excretion rates of sodium and potassium, osmolality clearance and free water clearance in CHF patients treated with ACE-inhibitors[61]. The presence of renal disease might represent a contra-indication to NSAIDs use. Whelton et al[62] reported how almost 30% of patients with renal disease have a relevant risk of worsening renal function when exposed to non-selective NSAIDs. However, the effects of NSAIDs on progression of chronic kidney disease need to be better clarified. A recent Canadian study performed in an elderly community – based cohort[63] demonstrated that patients treated with high dose of NSAID consumption presented an increased risk for rapid chronic kidney disease progression (26% increased risk for decreased in estimated GFR). No differential risk was to be found between non-selective and selective NSAID users. For this reason neither non-selective nor selective COX-2 inhibitors should be administered to patients with chronic renal disease. Two case-control studies carried out to identify the risk of renal adverse effects in elderly patients have been published[58-64]. Griffin et al[58] report a relevant increased risk of acute renal failure (58%) in current NSAID users. The risk of intrinsic renal failure is present only in patients with chronic renal failure, while the risk of pre-renal failure is independent from the presence of chronic renal disease. Ibuprofen, indomethacin, piroxicam, ketoprofen, fenoprofen would seem to present a high risk of renal failure (odds ratio >1.5) which increases on a par with drug dosage. On the contrary, naproxen and nonaspirin salicylates would seem to present a low risk (odds ratio <1) seemingly not correlated to the dose employed. Diclofenac and sulindac would seem to present an intermediate risk (Odd's ratio 1.40 and 1.47 respectively). The contemporary use of two or more NSAIDs exposes patients to the highest risk of renal failure (Odd's ratio 3.35)[58].

A study conducted on a general population aged between 50 to 84 years in the United Kingdom[64] reported a 3-fold greater risk of developing a first-ever diagnosis of clinical ARF in NSAID users compared to non-NSAID users. Meloxicam, more selective for COX-2 than traditional NSAIDs, features a higher risk compared to diclofenac and naproxen. The contemporary use of cardiovascular drugs and NSAIDs and diuretics or calcium channel blockers exposes patients to a greater risk (relative risk 11.6 and 7.8 respectively). Long term NSAID therapy together with high drug doses elicits a slight increase in this risk. On commencing NSAID treatment, no increased risk of ARF was observed. These results are in contrast with the above-mentioned study[58], although the actual reasons underlying these differences are not clear. As stated by the Authors, the characteristics of the populations investigated in the two studies may have differed. In fact, in the study performed by Griffin et al[58] the patients were older and all hospitalized. It might be argued that the incidence of renal adverse effects produced by non-selective NSAIDs is age-dependent and closely related to renal perfusion. Accordingly, use of these drugs should be avoided in the elderly and in patients affected by heart failure, hypertension, diabetes and chronic renal disease. The use of NSAIDs for topical application is generally considered to be safe because of the marginal percutaneous absorption (5-8%)[65]. Nevertheless, several cases of acute renal failure have been reported following topical NSAID treatment. In particular, we found three case reports of acute renal failure manifested after the use of ketoprofen, ibuprofen and piroxicam, respectively[65-67]. The mechanism of these events has not been well established, likely being elicited via an allergic mechanism.

To clarify the actual renal safety profile of COX-2 inhibitors, Zhang et al.[68] carried out a meta-analysis on 114 informative reports focusing on celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib and lumiracoxib. The study showed a significant heterogeneity regarding renal events produced by various agents, exhibiting no class effect of COX-2 inhibitors. These findings are of extreme importance in view of the fact that previous studies had supported the presence of a class

effect. Furthermore, following these findings the physician was given greater liberty in prescribing coxib treatment best suited to clinical conditions of patients. Rofecoxib significantly increased the risk of composite renal events (relative risk 1.53), including significantly elevated risks for peripheral oedema, hypertension and renal dysfunction (relative risk 1.43, 1.55, and 2.31, respectively). The use of higher doses and longer treatment duration increased the renal risk associated with rofecoxib. Valdecoxib and parecoxib are considered to increase the rate of renal adverse effects (relative risk 1.24). No other COX-2 inhibitors significantly increased the risk of renal adverse effects (relative risk 1.05 and 1.07 for etoricoxib and lumiracoxib, respectively). Celecoxib was associated with reduced rates of composite renal dysfunction (relative risk 0.97), hypertension and renal dysfunction (relative risk 0.83 and 0.61, respectively). The limits imposed by this meta-analysis cannot be extended to investigate the impact of patient comorbidity with conditions such as underlying chronic renal failure, on the safety of coxib administration. Secondly, additional studies should be performed to assess the actual safety profile of etoricoxib and lumiracoxib, in view of the scarce number of trials performed to date to this regard.

The elderly presents a higher risk of acute renal failure following coxib treatment than younger subjects, in agreement to findings observed with non-selective NSAIDs[69]. Indeed, coxibs are not indicated for use in patients with cardiovascular and renal disease. Side effects are manifested in correlation to the administered dose; accordingly, the use of high doses of COX-2 inhibitors in the elderly should be avoided. Patients should be monitored regularly in order to prevent the onset of side effects related to concomitant illness or new drug prescriptions[70]. Blood pressure should be monitored for all patients undergoing coxib therapy. On registering a significant increase in blood pressure, coxib treatment should be immediately withdrawn and substituted for another analgesic and also an increase of blood pressure should be treated immediately. The appropriate dosage of COX-2 inhibitors in order to avoid renal adverse effects has not yet been identified. However, it is reasonable to maintain that daily doses of rofecoxib 25 mg, celecoxib 200 mg and etoricoxib 90 mg should not increase the risk of renal failure either in healthy or elderly patients.

In recent years several published case reports have revealed how renal adverse effects are also associated with administration of COX-2 selective inhibitors[71,72]. Both celecoxib (200 mg /day) and rofecoxib (25 mg/day) induced the onset of acute interstitial nephritis. Management of these cases consisted in immediate withdrawal of coxib, although renal function was not completely restored in all cases.

Although administration of NSAIDs for chronic pain is strongly opposed by physicians, these drugs are massively employed in the management of postoperative pain. The incidence of postoperative renal failure related to NSAID use is a very rare event and has not yet been well established, being estimated, however, in the range of 0.001 to 0.1%[73]. A review published in 2007[73] investigated the effect of NSAIDs on postoperative renal function in patients with normal preoperative function. The study included 23 trials investigating 1459 patients, resulting in the finding of NSAID-induced slight, transient negative effects on kidney function in adults without previous renal disease. No cases of acute renal failure or severe renal failure or severe renal impairment were reported in the trials.

Finally, the use of NSAIDs for the treatment of postoperative pain is considered to be safe, although a few considerations should be made.

First, a marked difference is observed in the incidence of renal adverse effects between chronic surgical and non-surgical chronic patients. Postoperative patients are likely better-assisted, more careful attention being paid to prevent renal hypoperfusion and maintaining adequate renal blood flow.

Second, renal adverse effects are not necessarily related to the duration of NSAID administration, indeed, acute renal failure may occur even after a few days of intake.

The topics mentioned above are still object of controversies. As stated by Myles and Power[74] in 1998, “there needs to be continued research and the most efficient method for answering these questions are large, epidemiological case-control or cohort studies”.

Finally in the reference to pharmacological prevention of NSAID-induced renal toxicity, several Authors have proposed the use of nitric oxide (i.e. arginine) donors[75]. Furthermore, other studies suggest oxidative phosphorilation by the drug itself and an additional potential mechanism of overcoming NSAID-induced nephrotoxicity[75,76].

Conclusions

Historically, clinical advances registered in the nineteenth and twentieth centuries led to development of NSAIDs[77].

Nowadays NSAIDs represent the most widely used drug in medical practice. Indeed, the use of this class of compounds has increased dramatically during the recent years among patients of all ages, ranging from the newborn to the adults. Their use during pregnancy has also increased, in spite of the emerging findings: even short-term administration of NSAIDs during the late pregnancy period is correlated with a significant increase in risks of premature closure of ductus arteriosus[78].

It is very interesting to note that selective COX-2 inhibitors, often prescribed during pregnancy, are capable of crossing into the placenta although these compounds are not used in the new born[79]. According to the opinion of the Author and to the current literature, ibuprofen should represent the therapeutic option of choice during the neonatal period because of its lower nephrotoxic potential[80].

On the basis of the specific mechanism involved in the activation, NSAID nephrotoxicity should be considered as significant adverse effect, in particular in high risk patients of all ages. Similar to many of many other cases of drug-induced renal damage, acute renal failure is often initially non-oliguric. Thus, monitoring of renal function and serum creatinine levels is mandatory during therapy, together with assessment of electrolytes and blood pressure[81]. In particular, a novel approach for early and sensitive detection of NSAID- induced nephrotoxicity in newborns, based on the monitoring of urinary PGE2, has been successfully used[82].

Other biomarkers of early glomerular (such as cystatin C) or tubular damage will probably become increasingly involved in the future[83].

No effort should be spared in attempting to prevent unnecessary administration of NSAIDs, especially in high risk patients (Table III) such as patients with hypovolemia and/or pre-existing renal problems. These efforts should include the choice of compounds having a lower nephrotoxic potential, identification of the most appropriate dosage, avoiding concomitant administration of other nephrotoxic drugs, providing for early diagnosis of nephrotoxicity, and by limiting the duration of the treatment. However, it should be underlined how additional iatrogenic damage can often be prevented through immediate interruption of the administration of the drug, considering largely reversibility of the nephrotoxicity induced by the drug.

Table III. Selected risk factors for NSAIDs-induced acute nephrotoxicity.

Perinatal age
- Multiple pregnancies (especially monochorionic twin pregnancies)
- Prolonged and cumulative doses
- Short term between treatment and delivery
- Genetic factors
- Low birthweight
- Concomitant drugs (aminoglycosides, glycopeptides, diuretics)

Pediatric age
- Dehydration
- Hypovolemia
- Haemorrhage
- Congestive heart failure
- Liver failure
- Pre-existing renal problems
- Urinary tract malformations
- Recurrent urinary tract infections
- NSAIDs multitherapy
- Concomitant drugs (beta-blockers, ACE inhibitors, diuretics, aminoglycosides)
- Alcohol consumption
- Cystic fibrosis

Adult age
- Elderly
- Renal disease
- NSAIDs multitherapy
- Concomitant drugs (inotropes, calcium channel blockers, diuretics)
- Prolonged therapy

Particular caution should be taken in the handling of newly developed NSAIDs, particularly off-label or unlicensed products.

Future research in this field should be undertaken to focus on the actual role of NSAIDs in clinical practice for each age group, concentrating particularly on pregnant women.

Over-the-counter analgesics are usually deemed to be safe to use. However, patients using this type of medication without first consulting their physician may not be aware of potential hazards and predisposing factors aggravating adverse effects.

Ongoing medical education focusing on the interaction of NSAIDs with other drugs in terms of nephrotoxicity is mandatory[84].

Lastly, additional medical information listing the disadvantages and drawbacks of these drugs should be made available, bearing in mind that *pharmakon* means poison in ancient Greek.

References

1) Clyman RI. Medical treatment of patent ductus arteriosus in premature infants. In: Long WA, editor. Fetal and neonatal cardiology. WB Saunders, Phyladelphia, 1990: pp. 682-690.

2) Garella S. Drug-induced renal disease. Hosp Pract 1993; 15: 129-140.

3) Antonucci R, Cuzzolin L, Arceri A, Fanos V. Urinary prostaglandin E2 in the newborn and infant. Prostag Oth Lipid Mediat 2007; 84: 1-13.

4) Johnson AG. NSAIDs and increased blood pressure. What is clinical significance? Drug Safety 1997; 17: 277-289.

5) Crofford LJ. COX-1 and COX-2 tissue expression: implications and predictions. J Rheumatol Suppl 1997; 49: 15-19.

6) Komhoff M, Jeck ND, Seyberth HW, Grone HJ, Nusing RM, Breyer MD. Cyclooxygenase-2 expression is associated with the renal macula densa of patients with Bartter- like syndrome. Kidney Int 2000; 58: 2420-2424.

7) Adegboyega PA, Ololade O. Immunohistochemical expression of cyclooxygenase-2 in normal kidneys. Appl Immunohistochem Mol Morphol 2004; 12: 71-74.

8) Komhoff M, Wang JL, Cheng HF, Langenbach R, McKanna JA, Harris RC, Breyer MD. Cyclooxygenase-2 selective inhibitors impair glomerulogenesis and renal cortical development. Kidney Int 2000 b; 57: 414-422.

9) Slater D, Dennes W, Sawdy R, Allport V, Bennett P. Expression of cyclooxygenase types-1 and -2 in human fetal membranes throughout pregnancy. J Mol Endocrinol 1999; 22: 125-130.

10) Sawdy R, Slater D, Fisk N, Edmonds DK, Bennett P. Use of a cyclo-oxygenase type-2-selective non-steroidal anti-inflammatory agent to prevent preterm delivery. Lancet 1997; 350: 265-266.

11) Narumiya S, Sugimoto Y, Ushikubi F. Prostanoid receptors: structures properties and functions. Physiol Rev 1999; 79: 1193-226.

12) Vane, JR, Botting RM. Mechanisms of action of nonosteroidal anti- inflammatory drugs. Am J Med 1998, 104: 2S-8S.

13) Kaplan BS, Restaino I, Raval DS, Gottlieb RP, Bernstein J. Renal failure in the neonate associated with in utero exposure to non-steroidal antiinflammatory agents. Pediatr Nephrol 1994; 8: 700-704.

14) Ishibashi R, Tanaka I, Kotani M, Muro S, Goto M, Sugawara A, Mukoyama M, Sugimoto Y, Ichikawa A, Narumiya S, Nakao K. Roles of prostaglandin E receptors in mesangial cells under high-glucose conditions. Kidney Int 1999; 56: 589-600.

15) Boie Y, Stocco R, Sawyer N, Slipetz DM, Ungrin MD, Neuschäfer-Rube F, Püschel GP, Metters KM, Abramovitz M. Molecular cloning and characterization of the four rat prostaglandin E2 prostanoid receptor subtypes. Eur J Pharmacol 1997; 340: 227-241.

16) Breyer MD, Breyer RM. Prostaglandin receptors: their role in regulating renal function. Curr Opin Nephrol Hypertens 2000; 9: 23-29.

17) Moise KJ Jr. Effect of advancing gestational age on the frequency of fetal ductal constriction in association with maternal indomethacin use. Am J Obstet Gynecol 1993; 168: 1350-1353.

18) Wurtzel D. Prenatal administration of indomethacin as a tocolytic agent: effect on neonatal renal function. Obstet Gynecol 1990; 76: 689-692.

19) Norton ME, Merrill J, Cooper BA, Kuller JA, Clyman RI. Neonatal complications after the administration of indomethacin for preterm labor. N Engl J Med 1993; 329: 1602-1607.

20) Souter D, Harding J, McCowan L, O'Donnell C, McLeay E, Baxendale H. Antenatal indomethacin-adverse fetal effects confirmed. Aust NZ J Obstet Gynecol 1998; 38: 11-16.

21) Itskovitz J, Abramovici H, Brandes JM. Oligohydramnios, meconium and perinatal death concurrent with indomethacin treatment in human pregnancy. J Reprod Med 1980; 24: 137-140.

22) 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: 252-257.

23) 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: 371-373.

24) Veersema D, De Jong PA, Van Wijck JA. Indomethacin and the fetal renal non function syndrome. Eur J Obstet Gynecol Reprod Biol 1983; 16: 113-121.

25) Jacqz-Aigrain E, Guillonneau M, Boissinot C, Bavoux F, Hartmann JF, Blot P. Maternal and neonatal effects of indomethacin administrated during pregnancy. Apropos of 18 cases. Arch Fr Pediatr 1993; 50: 307-312.

26) van der Heijden BJ, Carlus C, Narcy F, Bavoux F, Delezoide AL, Gubler MC. Persistent anuria, neonatal death and renal microcystic lesions after prenatal exposure to indomethacin. Am J Obstet Gynecol 1994; 171: 617-623.

27) 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 Trasplant 1996; 11: 1139-1141.

28) 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: 467-473.

29) Hamrick SE, Hansmann G. Patent ductus arteriosus of the preterm infant. Pediatrics 2010; 125: 1020-1030.

30) Stefano JL, Abbasi S, Pearlman SA, Spear ML, Esterly KL, Bhutani VK. Closure of the ductus arteriosus with indomethacin in ventilated neonates with respiratory distress syndrome: effects on pulmonary compliance and ventilation. Am Rev Respir Dis 1991; 143: 236-239.

31) Ohlson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (review). Cochrane Database Syst Rev 2010; 4:CD003481.

32) Benitz WE. Treatment of persistent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol 2010; 30: 241-252.

33) Patel J, Marks KA, Roberts I, Azzopardi D, Edwards AD. Ibuprofen treatment of patent ductus arteriosus. Lancet 1995; 346: 255.

34) Kuo CY. Treatment of patent ductus arteriosus with low-dose indomethacin in very low birth weight neonates with impairment of renal function: report of three cases. J Perinatol Med 1996, 24: 657-660.

35) Laudignon N, Chemtob S, Bard H, Aranda JV. Effect of indomethacin on the cerebral blood flow velocity of premature newborns. Biol Neonate 1988; 54: 254-262.

36) Aranda JV, Varvarigou A, Beharry K, Bansal R, Bardin C, Modanlou H, Papageorgiou. Pharmacokinetics and protein binding of intravenous ibuprofen in premature newborn infants. Acta Pediatr 1997; 86: 289-293.

37) Fajardo CA, Whyte RK, Steele BT. Effect of dopamine on failure of indomethacin to close the patent ductus arteriosus. J Pediatr 1992; 121: 771-775.

38) Sakhalkar VS, Merchant RH. Therapy of symptomatic patent ductus arteriosus in preterms using mefenamic acid and indomethacin. Indian Pediatr 1992; 29: 313-318.

39) 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: 886-891.

40) Aranda JV, Varvarigou N, Beharry K, Modanlou H, Bardin C, Papageorgiou A. The effect of early intravenous ibuprofen on renal function in premature newborns. Pediatr Res 1994; 37: 361A.

41) Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA 1996; 275: 539-44.

42) Van Overmeire B, Follens I, Hartmann S, Creten WL, Van Acker KJ. Treatment of patent ductus arteriosus with ibuprofen. Arch Dis Child 1997; 76: 179-184.

43) Zaffanello M, Brugnara M, Bruno C, Franchi B,Talamini G, Guidi G, Cataldi L, Biban P, Mella R, Fanos V. Renal function and volume of infants born with a very low birth weight: a preliminary cross-sectional study. Acta Paediatr 2010; 99: 1192-1198.

44) McIntire SC, Rubenstein RC, Gartner JC Jr, Gilboa N, Ellis D. Acute flank pain and reversible renal dysfunction associated with nonsteroidal anti-inflammatory drug use. Pediatrics 1993; 92 : 459-460.

45) Lesko SM, Mitchell AA. Renal function after short term ibuprofen use in infants and children. Pediatrics 1997; 100: 954-957.

46) van Biljon G. Reversible renal failure associated with ibuprofen in a child: a case report. S Afr Med J 1989; 76: 34-5.

47) Schaller S, Kaplan BS. Acute nonoliguric renal failure in children associated with nonsteroidal anti-inflammatory agents. Pediatr Emerg Care1998; 14: 416-418.

48) Simckes AM, Chen SS, Osorio AV, Garola RE, Woods GM. Ketorolac-induced irreversible renal failure in sickle cell disease: a case report. Pediatr Nephrol 1999; 13: 63-67.

49) Kim J, Gazarian M,Verjee Z, Johnson D. Acute renal insufficiency in ibuprofen overdose. Pediatr Emerg Care 1995; 11: 107-108.

50) Kelly MT, Walson PD, Hayes JR, Edge JH. Safety of paracetamol and ibuprofen in febrile children. Drug Invest 1993; 6: 48-55.

51) Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen: a practitioner-based randomized clinical trial. JAMA 1995; 273 : 929-933.

52) Moghal NE, Hulton SA, Milford DV. Care in the use of ibuprofen as an antipyretic in children. Clin Nephrol 1998; 49: 293-295.

53) Kovesi TA, Swartz R, MacDonald N. Transient renal failure due to simultaneous ibuprofen and amynoglycoside therapy in children with cystic fibrosis. N Engl J Med 1998; 338: 65-66.

54) Brater DC. Anti-inflammatory agents and renal function. Semin Arthritis Rheum 2002; 32: 33-42.

55) Cheng HF, Harris RC. Renal effects of non-steroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors. Curr Pharm Design 2005; 11: 1795-1804.

56) Gambaro G, Perazella MA. Adverse renal effects of anti-inflammatory agents: evaluation of selective and nonselective cyclooxigenase inhibitors. J Intern Med 2003; 253: 643-652.

57) Galli G, Panzetta G. Case report: reversible acute renal failure following therapy with both ketorolac (non-selective non-steroidal anti-inflammatory drug NSAID) and celecoxib (COX-2 selective) in the same patient. G It Nefrol 2002; 19: 199-203.

58) Griffin MR, Yared A, Ray WA. Nonsteroidal anti-inflammatory drugs and acute renal failure in elderly persons. Am J Epidemiol 2000; 15: 488-496.

59) Weir MR. Renal effects of nonselective NSAIDs and coxibs. Cleve Clin J Med. 2002; 69: S153-158.

60) Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM; SUCCESS VI Study Group. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomiszed, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther 2001; 8: 85-95.

61) Juhlin T, Björkman S, Gunnarsson B, Fyge A, Roth B, Höglund P. Acute administration of diclofenac, but possibly not long term low dose aspirin, causes detrimental renal effects in heart failure patients treated with ACE-inhibitors. Eur J Heart Fail 2004; 6: 909-916.

62) Whelton A, Stout RL, Spilman PS, Klassen DK. Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure. A prospective, randomized, crossover comparison. Ann Intern Med 1990; 112: 568-576.

63) Gooch K, Culleton BF, Manns BJ, Zhang J, Alfonso H, Tonelli M, Frank C, Klarenbach S, Hemmelgarn BR. NSAID use and progression of chronic kidney disease. Am J Med 2007; 120: 280.e1-280.e7.

64) Huerta C, Varas-Lorenzo C, Castellsague J, García Rodríguez LA. Non-steroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population. Heart 2006; 92: 1610-1615.

65) Krummel T, Dimitrov Y, Moulin B, Hannedouche T. Acute renal failure induced by topical ketoprofene. Br Med J 2000; 320: 93.

66) O'Callaghan CA, Andrews PA, Ogg CS. Renal disease and use of topical non-steroidal: anti-inflammatory drugs. Br Med J 1994; 308: 110-111.

67) Fernando AH, Thomas S, Temple RM, Lee HA. Renal failure after topical use of NSAIDs. Br Med J 1994; 308: 533.

68) Zhang J, Ding EL, Song Y. Adverse effects of cyclooxigenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. JAMA 2006; 296: 1619-1632.

69) Schneider V, Levesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs the acute renal failure: a population-based, nested case-control analysis. Am J Epidemiol 2006; 164: 881-889.

70) Savage R. Cyclo-oxigenase-2 inhibitors: when should they be used in the elderly? Drug Aging 2005 22: 185-200.

71) Almansori M, Kovithavongs T, Qarni MU. Cyclooxigenase-2 inhibitor-associated minimal-change disease. Clin Nephrol 2005; 63: 381-384.

72) Esteve JB, Launay-Vacher V, Brocheriou I, Grimaldi A, Izzedine H. COX-2 inhibitors and acute interstitial nephritis: case report and review of the literature. Clin Nephrol 2005; 63: 385-389.

73) Lee A, Cooper MC, Craig JC, Knight JF, Keneally JP. Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. Cochrane Database Syst Rev 2007; CD002765.

74) Myles PS, Power I. Does ketorolac cause postoperative renal failure: how do we assess the evidence? Brit J Anaesth 1998; 80: 420-421.

75) Basivireddy J, Jacob M, Pulimood AB, Balasubramanian K. A Indomethacin-induced renal damage: role of oxygen free radicals. Biochem Pharmacol 2004; 67: 587-599.

76) Hichey EJ, Raje RR, Reid VE, Gross SM, Ray SD. Diclofenac induced in vivo nephrotoxicity may involve oxidative stress-mediated massive genomic DNA fragmentation and apoptotic cell death. Free Radic Biol Med 2001: 31 139-152.

77) Rainsford KD. Anti-inflammatory drugs in the 21st century. Subcell Biochem 2007; 42: 3-27.

78) Koren G, Florescu A, Costei AM, Boskovic R, Moretti ME. Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. Ann Pharmacother 2006; 40: 824-829.

79) Fornaro M, Cuzzolin L, Fanos V. Renal tolerability of non-steroidal drugs (NSAIDS) in newborn infants. Pediatr Med Chir 2004; 26: 423-429.

80) 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: 187-193.

81) Schetz M, Dasta J. Goldstein S, Golper T. Drug-induced acute kidney injury. Curr Opin Crit Care 2005; 11: 555-565.

82) 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: 223-230.

83) Zaffanello M, Franchini M, Fanos V. Is serum cystatin-C a suitable marker of renal function in children? Ann Clin Lab Sci 2007; 37: 233-240.

84) Hersh EV, Pinto A, Moore PA. Adverse drug interactions involving common prescription and over-the-counter analgesic agents. Clin Ther 2007; 29(Suppl): 2477-2479.

85) Becker-Cohen R, Frishberg Y. Severe reversible renal failure due to naproxen- associated acute interstitial nephritis. Eur J Pediatr 2001; 160: 293-295.

86) Ulinsky T, Guigonis V, Dunan O, Bensman A. Acute renal failure after treatment with non-steroidal anti-inflammatory drugs. Eur J Pediatr 2004; 163: 148-150.

87) Krause I, Cleper R, Eisenstein B, Davidovits M. Acute renal failure, associated with non-steroidal anti-inflammatory drugs in healthy children. Pediatr Nephrol 2005; 20: 1295-1298.

88) Fletcher JT, Graf N, Scarman A, Saleh H, Alexander SI. Nephrotoxicity with ciclooxygenase 2 inhibitor use in children. Pediatr Nephrol 2006; 21: 1893-1897.