

Acute nephrotoxicity of NSAID from the foetus to the adult

M. MUSU¹, G. FINCO¹, R. ANTONUCCI², E. POLATI³, D. SANNA¹,
M. EVANGELISTA⁴, D. RIBUFFO⁵, V. SCHWEIGER³, V. FANOS²

¹Department of Medicine "M. Aresu", University of Cagliari, Cagliari (Italy)

²Neonatal Intensive Care Unit, University of Cagliari, Cagliari (Italy)

³Department of Anesthesiology and Intensive Care, University of Verona, Verona (Italy)

⁴Department of Emergency, Catholic University of the Sacred Heart, Rome (Italy)

⁵Department 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 treatment¹ 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 population². 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 conditions³. In addition to their role in inflammation, prostaglandins regulate a

variety of renal functions such as vascular tone, salt and water balance, and renin release⁴.

COX-1 is constitutively expressed in several tissues and is thought to participate in “house-keeping” 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 flow⁵.

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 kidneys⁵. 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 MD⁶. In human kidney, COX-2 expression has been reported to be present in podocytes and arteriolar smooth muscle cells⁷. 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 cortex⁸. 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 recta⁷.

COX-2 seems to be involved in the regulation of glomerular haemodynamics, and has been demonstrated to play a major role in nephrogenesis⁸.

Slater et al⁹ studied the expression of the 2 COX isoforms in human foetal membranes throughout pregnancy and reported that an up-regulation 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 agent¹⁰.

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 function¹¹.

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 activity¹². NSAID treatment may precipitate renal failure in susceptible individuals and cause severe, albeit rare, complications in infants exposed to NSAIDs in utero¹³. 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 vasoconstrictor¹⁴. 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 effect¹⁵. 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 effects¹⁶.

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' gestation¹⁷. 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 post-natal 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 inhibitors¹⁸. 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 haemorrhage, necrotising enterocolitis and PDA¹⁹. 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 indomethacin²⁰. Itskovitz et al²¹, 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 therapy²²⁻²⁴. Five of 23 neonates born after prenatal exposure to

indomethacin developed transient renal insufficiency²⁵.

More recently, Van der Heijden et al²⁶ reported that 6 neonates exposed to indomethacin in utero for at least 5 weeks died of anuria. Pomeranz et al²⁷ 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 utero²⁸.

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 reviewed very recently²⁹. Treatment of PDA with NSAIDs, through the inhibition of prostaglandin synthesis, is indicated before left to right ductal shunting occurs³⁰ and a recent 3rd Cochrane review has been dedicated to this argument³¹. Benitz³² very recently greatly criticised contemporary therapeutic 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 treatment¹ and prophylaxis³³ of PDA in premature neonates. However, adverse effects such as transient or permanent alterations in renal function³⁴, necrotising enterocolitis¹⁹, gastrointestinal haemorrhage³⁴, and impairment of cerebral blood flow³⁵ 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 weeks³⁶. 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 successful³⁷. Other NSAIDs have

Table 1. 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 acid³⁸ or to be less effective than indomethacin at closing the duct, as in the case of acetylsalicylic acid³⁹.

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 cerebral³³ and renal adverse effects⁴⁰. Recently its prophylactic use, although not yet uniformly accepted, has been advocated. In a phase I trial, Vargarigou et al⁴¹, 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 al⁴² 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 extremely 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 drug⁴⁴. Children may be at great risk of nephrotoxicity in some conditions like dehydration accompanying fever, the most common paediatric indication for NSAID treatment⁴⁵.

Adverse effects associated with NSAID use in children are renal failure, metabolic acidosis, hypocalcemia, acute flank pain and interstitial nephritis⁴⁶⁻⁴⁹.

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) recipients⁵⁰. In a randomised trial involving 83,915 children⁵¹, 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 population⁴⁵ 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 al⁵² 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 reported⁵³ 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, hyperkalemia and hypertension^{54,56,57}.

Renal adverse effects elicited by NSAIDs are dose-dependent⁵⁸. 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 varying 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	Interstitial 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 nephrosis⁵⁹, 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-inhibitors⁶⁰.

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-inhibitors⁶¹. The presence of renal disease might represent a contra-indication to NSAIDs use. Whelton et al⁶² 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 cohort⁶³ 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 published⁵⁸⁻⁶⁴. Griffin et al⁵⁸ 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 Kingdom⁶⁴ 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 study⁵⁸, 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 al⁵⁸ 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, respectively⁶⁵⁻⁶⁷. 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 NSAIDs⁶⁹. 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 prescriptions⁷⁰. 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 2007⁷³ 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 Power⁷⁴ 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) donors⁷⁵. Furthermore, other studies suggest oxidative phosphorylation 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 NSAIDs⁷⁷.

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 arteriosus⁷⁸.

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 newborn⁷⁹. 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 potential⁸⁰.

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 pressure⁸¹. 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 used⁸².

Other biomarkers of early glomerular (such as cystatin C) or tubular damage will probably become increasingly involved in the future⁸³.

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

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

often be prevented through immediate interruption of the administration of the drug, considering largely reversibility of the nephrotoxicity induced by the drug.

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 mandatory⁸⁴.

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.

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