Drug-Induced Nephrotoxicity In The Newborn: The State Of The Art

VASSILIOS FANOS*, ROBERTO ANTONUCCI*, MICHELE MUSSAP°, MARCO ZAFFANELLO°

*Department of Paediatrics, Neonatal Intensive Care Unit, Puericultura Institute and Neonatal Section University of Cagliari, ITALY

○ Department of Laboratory Medicine, University-Hospital, Genova, ITALY

°Department of Mother-Child and Biology-Genetics, University of Verona, ITALY

vafanos@tiscali.it – www.patologianeonatalecagliari.it

Abstract: - The kidney is vulnerable to drugs because of its high blood flow and large capillary surface area, its role as the excretory route for many drugs and its detoxifying action. Glomeruli, tubules, interstitium and arterioles may be altered. It is important for the neonatologist to recognize the problem of drug-induced kidney injury because the causative agents are very commonly prescribed, nephrotoxicity is frequent and reversible in many patients. Drug-induced renal failure is often non-oliguric. Early diagnosis of nephrotoxicity is essential since dosage adjustment or discontinuation of renally excreted drugs may prevent further iatrogenic damage. Thus monitoring of renal function is essential and prevention is mandatory.

Key words: Newborn, drugs, acute kidney injury, diagnosis, prevention

1. Introduction

One of the major functions of the kidney is the concentration of toxic metabolites and drugs. Thus it is a frequent site of drug toxicity. The glomeruli, tubules, interstitium and arterioles may be altered. Iatrogenic complications include acute kidney failure (ARF): prerenal, renal or postrenal which are frequently reversible when diagnosed early. Drug-induced kidney disease is frequent in all age groups [1,2]. In the paediatric kidney the incidence seems lower if compared with adults. Drugs have also been found to be involved in 50% of cases of ARF in premature newborn. Recent data suggest in preterm neonates a significant role for maternal consumption and postnatal administration of nonsteroidal anti-inflammatory drugs (NSAIDs) in preterm infants [3,4].

Many factors make the kidney particularly susceptible and vulnerable to toxic damage: the high renal blood flow (renal blood flow accounts for 25% of cardiac output), the predominantly renal excretion of many drugs, the large capillary surface area, the high degree of specialisation of the proximal tubule cells, the progressive concentration of filtered and secreted compounds in the tubular lumen.

Discussion of drug-induced nephrotoxicity must consider some important points that are presented below.

A drug may give rise to renal damage in different parts of the nephron and different drugs can have the same intracellular target [5].

Many nephrotoxins are taken up by the renal target cell, where they are effectively capable of exerting the damage: the proximal tubule is generally to be regarded as the target structure [6].

The nephronic heterogeneity (internephronic, intranephronic and intrasegmental) influences the type of cell damage. In particular, anatomical, physiological and biochemical differences within the nephron may explain the damaging effects of some drugs.

A number of concurrent pathophysiological mechanisms often act in unison such as reduction of renal perfusion, direct tubular toxicity, immunomediated toxicity, interference with fluids and electrolytes.

Vulnerability is related to patient age and it is considered less frequent and severe in newborns than in adults but this subject is controversial. The main hypotheses comprise: a different ratio of renal volume/corporeal volume (i.e. higher in the neonate); less interception of the drug (i.e. aminoglycoside) by the proximal tubular cells; and less sensitivity of the immature tissue towards the toxins [6]. However, neonatal status may itself be a risk factor for drug-induced nephrotoxicity. In fact, it has been confirmed that low birthweights contribute to development of renal disease [7,8].
The effects of maternally administered drugs on the fetal and neonatal kidney have been well documented and reviewed [9]. The actual importance of drugs as causes of nephrotoxicity is not easy to define: in fact the drugs are administered to newborns and children who are sick and often seriously ill, who present haemodynamic abnormalities and/or electrolyte derangements. All these situations may be important co-factors in bringing about the renal damage [10].

Adverse renal effects of drugs on the kidney are silent, especially in early stages and clinical vigilance is needed. Moreover early diagnosis of nephrotoxicity is essential since dosage adjustment or discontinuation of renally excreted drugs may prevent further iatrogenic damage because most drug nephrotoxicity is reversible [11].

A take-home message is that drug-induced renal failure is often non-oliguric. Thus monitoring of renal function is mandatory during potentially nephrotoxic therapies [12]. A special problem is represented by newborns and infants with urinary tract malformations undergoing long term antibiotic prophylaxis [13].

Drug-induced nephrotoxicity (namely due to AMG) was defined clinically in terms of an increase in serum creatinine (Crs) more than 20% in relation to baseline values. A review of early diagnosis of Acute Kidney Injury with urinary biomarkers and with cystatin C in the newborn has been recently published by ours [14].

In the present paper we are going to discuss the nephrotoxicity associated with drugs commonly used in the newborn: antibiotics (aminoglycosides, glycopeptides, cephalosporins, carbapenems, antifungals, nonsteroidal anti-inflammatory drugs).

2. Early diagnosis of Acute Kidney Injury with urinary biomarkers in the newborn

“Acute Kidney Injury (AKI)” has recently become the preferred term to describe the syndrome of acute renal failure (ARF), while the term “Failure” is restricted to patients who have AKI and need renal replacement therapy [15-17].

Early diagnosis of AKI is often problematic due to a lack of suitable biomarkers of renal damage. Currently, AKI is diagnosed tipically by measuring serum creatinine and urea levels and, less frequently, other urinary tests [18].

Unfortunately, creatinine is an unreliable indicator during acute changes in kidney function. In fact, the elevation of serum creatinine, with or without oliguria, does not enable an identification of renal damage early enough to make possible a successful intervention for various reasons. First, serum creatinine levels can vary widely with age, gender, lean muscle mass, muscle metabolism, and hydration status. Second, serum creatinine concentrations may not change until about 50% of kidney function has already been lost. Third, at lower rates of glomerular filtration, the amount of tubular secretion of creatinine results in overestimation of renal function. Finally, during acute changes in glomerular filtration, serum creatinine does not accurately depict kidney function until steady-state equilibrium has been reached, which may require several days [14,19].

In the neonatal period, other problems could contribute to delay and complicate the diagnosis of AKI [17]: a) interference of maternal values; b) endogenous (bilirubin) and exogenous chromogens (cephalosporins) interfering with Jaffe reaction; c) tubular reabsorption in preterm infants; d) evaluation of GFR only in equilibrium conditions.

Recently, cystatin C, a marker of glomerular function in the "creatinine blind" period, has been shown superior to conventional markers [20] and was also evaluated in the newborn [21-23].

Other newly characterized markers of kidney function such as neutrophil gelatinase-associated lipocalin (N-GAL), kidney injury molecule-1 (KIM-1) and interleukin-18 (IL-18) have the potential to improve the management of patients with AKI [24] and could be useful in the newborn. Genomic markers may also be helpful in toxic renal injury. In particular the tissue and urinary expression of kidney injury molecule-1, increases before creatinine and could serve as an early indicator of nephrotoxicity in rats [25]. Similarly a set of potential biomarkers with a time- and dose-response with respect to the progression of proximal tubular toxicity has been reported [26].

We recently reported our experience on metabolomics in diagnosing renal disease in children [27]. Also the metabolomics approach, together with transcriptomics and proteomics, will have substantial impact on diagnostics, therapeutics and drug development and may be an important new tool in neonatology [28].

3. Antibiotics
3.1 Aminoglycosides
Aminoglycosides (AMG) are still widely employed despite their low therapeutic index [29,30]. Gentamicin is probably the most studied drug-nephrotoxin. Among antibiotic-induced ARF, 80%
are related to the AMGs (60% in single-drug therapy and 20% in combination with cephalosporins [6]. The aminoglycosides are eliminated without metabolic transformation almost exclusively by the kidneys and via glomerular filtration. A small amount of aminoglycoside (5%) after glomerular filtration is transported into the tubular cells in the S1 and S2 segments (first step towards nephrotoxicity). Within the tubular cells high aminoglycoside concentrations occur in the lysosomes, and then interfere with protein reabsorption, protein synthesis in the endoplasmatic reticulum, mitochondrial respiration and sodium-potassium pump (second step towards nephrotoxicity) [6]. It has been demonstrated that glycoprotein 330 (gp 330), also called megalin, plays an important role in the aminoglycoside transport and accumulation [31].

The consequent structural damage may result in cell necrosis, and is associated with a corresponding microscopy finding in light (formation of multilaminated membrane structures: myeloid bodies) or electron microscopy. Myeloid bodies development within tubular cells lysosomes is the most characteristic early cytotoxic effect. By a clinical point of view after one or two days of aminoglycoside therapy a conspicuous urinary loss of microglobulins occurs (functional tubular damage). On the third day, a sharp increase in urinary enzymes is observed (structural tubular damage). After 6 days' therapy, cylindruria, proteinuria, polyuria and reduced urine concentration capacity may be present. It may occur earlier in the presence of other risk factors.

Aminoglycoside-induced tubulotoxicity is frequent, but is generally reversible on discontinuing the drug. The patient is usually nonoliguric. However it should be considered that renal damage may alter the pharmacokinetics of the drug, reducing renal excretion and creating dangerous vicious circles. The serum creatinine characteristically rise 5 to 10 days after the beginning of therapy, but other less frequent manifestations include an increased urinary excretion of sodium, potassium, magnesium, phosphorus, uric acid, amino acids and glucose. In selected cases there may be a fully Fanconi syndrome. Acute renal failure may appear only at a later stage.

Numerous factors intervene in bringing about aminoglycoside nephrotoxicity, such factors related to the antibiotic itself, those related to the patient and the associated pathology, as well as pharmacologic factors. They are presented below.

Aminoglycoside intrinsic toxicity. AMG-induced glomerular toxicity shows the following breakdown: gentamicin > tobramycin > amikacin > netilmicin [32]. The superior renal tubular tolerability of netilmicin was also confirmed in newborns with the employ of enzymuria.

Aminoglycoside administration modalities. Experimentally the modalities of AMG administration, continuous or intermittent infusion, once-daily administration (ODA) twice daily administration (TDA) or multiple daily doses (MDD) condition the renal accumulation kinetics (RAK) of AMGs and thus their nephrotoxicity. Experimentally gentamicin and netilmicin present saturaible RAK. Tobramycin, on the contrary, presents non-saturable RAK. In the case of amikacin, RAK is mixed, being saturaible at low serum concentrations and non-saturaible at high concentrations [33].

A meta-analysis also confirmed the lower nephrotoxicity of extended interval dosing compared with conventional dosing in children, including newborns [34].

High trough and peak levels: the therapeutic drug monitoring (TDM) has two major objectives: a) to ensure therapeutic concentrations b) to avoid toxicity. In adults patients therapeutic efficacy and toxicity well correlated with serum concentrations [35].

Most investigators relate the nephrotoxicity to high trough levels (measured immediately before the next administration of AMG). They should be kept below 10 mg/ml for amikacin and below 2 mg/ml for the other AMGs. Peak levels (obtained 30 minutes after a IV administration, 60 minutes after a IM administration) of GNT,TBR and NTM should be maintained at 5 to 8 mg/ml and for AMK at 15 to 25 mg/ml. Even if the necessity of routine therapeutic drug monitoring (TDM) in the first week of life has been questioned [36,37], neonates often require TDM and an individually adjusted therapeutic regimen, especially preterm infant [10,38]. However AMG nephrotoxicity can occur even with proper TDM.

Other risk factors: prolonged therapy, malnutrition, volume depletion, liver disease, preexisting renal disease, potassium and magnesium depletion, concomitant exposure to other nephrotoxic drugs such as amphotericin B, ciclosporin, vancomycin and NSAIDs are all risk factors. Clinical conditions commonly observed in the newborn that may amplify AMG nephrotoxicity are neonatal anoxia, respiratory distress syndrome and mechanical ventilation, hyperbilirubinaemia. Sepsis due to gram-negative bacteria is also associated with
AMG-induced kidney damage especially in presence of renal hypoperfusion, fever and endotoxinaemia [5].

3.2 Glycopeptides
The mechanism of vancomycin nephrotoxicity is not clear. The main mechanism is a tubular transport (energy-dependent) of the glycopeptide from blood to tubular cell across the basolateral membrane; similarly to some AMGs a saturation of this tubular transport would occur at a particular concentration [39].

There is an accumulation of vancomycin in the lysosomes of proximal tubular cells but it is not similar to the behaviour of AMG. Nephrotoxicity relates to the combined effect of a large area under the concentration-time curve and duration of therapy. A chronotoxicity of vancomycin has been observed with morning administration being associated with less toxicity than evening doses [40].

In most cases nephrotoxicity associated with vancomycin is reversible, even after high doses. Vancomycin-nephrotoxicity before 1980, observed in about of 25% od treated adults, is attributed to impurities present in the old preparations [41]. Nephrotoxicity was seen in 11% of children receiving vancomycin alone [42]. Risk factors related to vancomycin are high trough values (>10 mg/l) and prolonged therapy with patients being treated for periods >3 weeks [43]. There is no evidence that transient high peak concentration (>40mg/l) are associated with toxicity. However it is not clear whether elevated serum trough levels are the cause or the consequence of renal failure. High baseline serum creatinine concentration, liver disease, neutropenia and peritonitis are also considered significative risk factors [40].

An analysis of the literature shows that vancomycin-induced nephrotoxicity in newborns, infant and children is rare and often reversible and without clear relation to serum concentration . However the association AMG-vancomycin should be used with caution when an alternative combination is possible, when TDM of both drugs is impracticable, and in VLBW [44].

Teicoplanin nephrotoxicity, if compared with vancomycin, is lower [45] even in paediatrics [44]

3.3 Beta-Lactams
3.3.1 Cephalosporins
The nephrotoxicity of cephalosporins, depends substantially on 2 factors: a) the intra-cortical concentration of the drug; b) the intrinsic reactivity of the drug [46].

The intra-cortical concentration of the of the cephalosporin, depending on the equilibrium created at the tubule cell level between active transport, secretion and reabsorption is determinant for the development of nephrotoxicity. The importance of a antiluminal active organic acid transport is well known: a) nephrotoxicity due to cephalosporins is limited to the compounds trasported with this system; b) prevention of damage is possible inhibiting this transport; increasing the intracellular uptake of cephalosporin increases toxicity [47].

The intrinsic "reactivity" of the cephalosporins means its potential negative interaction with the intracellular targets, at 3 levels: a) lipid peroxidation; b) acylation and inactivation of tubule proteins; and c) competitive inhibition of mitochondrial respiration.

Cephaloridine and cephaloglycine are the only cephalosporins capable of causing kidney damage (involving the mitochondria) at therapeutic doses. Very recently transcriptomic data revealed several characteristic expression patterns of genes associated with specific cellular processes, including oxidative stress response and proliferative response, upon exposure to cephaloridine, which may enhance our understanding of the molecular mechanisms behind cephalosporin antibiotic-induced nephrotoxicity [48].

For all the other cephalosporins the renal damage can occur only at extremely high doses, much greater than the routine therapeutic doses [49]).

The decreasing nephrotoxicity of cephalosporins "in vivo" is cephaloglycine > cephaloridine > cefaclor > cephalozin > cephalothin >>> cephalaxin > ceftazidime. Generally third generation cephalosporins, widely used in pediatrics, give rise to a direct significant increase in serum creatinine in less than 2% of treated cases, with the exception of cefoperazone (5%) [50].

An interesting characteristic of cefotaxime is its low sodium content (about 1/5 and 1/4 of ceftazidime and ceftriaxone, respectively): this could be useful in newborns and children with hypernatremia and/or fluid overload [51].

As regards Crs it should be recalled that cephalosporins are capable of interfering with Jaffe reaction, which is the most commonly used technique for assaying creatinine in the blood and in urine.

3.3.2 Carbapenems
Carbapenems present a significative potential for nephrotoxicity, higher than cephalosporins and
penicillins. Together with cephaloridin and cephaloglycin, imipenem and panipenem are the most nephrotoxic beta-lactam compound [52]. Imipenem is hydrolysed at renal level by a brush-border enzyme (dehydropeptidase I) giving rise to more toxic and less active metabolites. Consequently imipenem is administered together with cilastatin, a specific inhibitor of dehydropeptidase I in a 1:1 ratio, which prevents nephrotoxicity. A lower potential for dehydropeptidase I in newborns receiving amoxicillin and cephalotaxine and/or furosemide have been suggested to prevent nephrotoxicity was observed with meropenem.

4. Antifungals

4.1 Amphotericin B

As regards as amphotericin B-induced nephrotoxicity, it is a result of different processes: these include the vehicle (deoxycholate) in which amphotericin is administered [53], ischemic injury due to a reduction of renal blood flow and GFR [54,55], increase in salt concentrations at the macula densa leading to enhanced stimulation of the tubuloglomerular feedback and vasoconstriction [56]. Interaction of amphotericin B with cholesterol on the human tubular cell membrane has also been postulated [55] and apoptosis in proximal tubular cells and medullary interstitial cells has been documented [57]. Acute renal failure, the most serious complication, is rare. More frequent is tubulotoxicity, which includes potassium and magnesium loss in urine, renal tubular acidosis and loss of urinary concentrating ability. Hypokalemia is common [6]. Risk factors include the amphotericin B cumulative dose, and the average daily dose, concomitant diuretics, abnormal baseline creatinine values and concomitant administration of potentially nephrotoxic drugs.

Informations on new lipid formulations of amphotericin B (ABLC-Amphotericin B Lipid Complex: Abelcet, Amphotec, and AmBisome) are limited in children and newborns. Lipid-based share a considerable reduction of nephrotoxicity in adults. Presently the use of such agents should be restricted to those who are intolerant of or refractory to AmB.

In neonates unlike from other ages, an increase in creatininemia seems not to be related to the total cumulative dose of the drug, and may appear after the first few doses. Discontinuation of treatment for a few days can lead to recovery. Amphotericin B should be used with caution in newborns receiving other nephrotoxic drugs, such as aminoglycosides. The concomitant administration of dopamine and/or furosemide have been suggested to prevent injury. However only salt loading has been clearly shown to ameliorate renal damage in humans. Hypokalemia may be so significant and require aggressive intravenous therapy, with possibly consequent hyperkalemia. Hypomagnesemia may give rise to refractory hypocalcemia.

4.2 Other antifungals

Alternative antifungals are currently available for use in newborns: the azoles (itraconazole, fluconazole, voriconazole), the fluorinated pyrimidines (flucytosine), the echinocandins (caspofungin, micafungin, anidulafungin). Among azoles fluconazole is by far the most widely used azole and has been reported to be relatively well tolerated. As regards renal tolerability, in an observational study of therapeutic fluconazole 6 mg/kg daily given to treat Candida sepsis, two of 40 babies developed raised serum creatinine levels, but none needed to stop treatment [58]. Several studies of prophylactic fluconazole did not report clinically important nephrotoxicity [59-62]. Data regarding safety of voriconazole in newborns and children are limited and mostly reported as case reports. In 3 of them no renal side-effects were noted, despite the developmentally limited renal function of the infant and the concurrent administration of other nephrotoxic drugs [63-65].

Flucytosine, due to the evidence of primary and acquired resistance in some strains, so it should not be used as monotherapy [66]. In preterm infants, it is used in combination with amphotericin B for its synergism and high penetration in the central nervous system. However, being available only for oral administration, its use in newborns is limited [67].

Regarding echinocandins, abnormalities in laboratory tests (serum creatinine and blood urea nitrogen elevations, hypokalemia) are uncommon, but rather more frequent with caspofungin, the first echinocandin approved in therapy [68], and usually administered to patients unresponsive to conventional antifungal therapies. Hesseling et al. [69] for the first time reported the use of caspofungin in an ELBW infant born at 24 wks gestation who developed a systemic candidemia and was unresponsive to amphotericin B and flucytosine: although the antifungal failed in this end-stage therapy, no side-effects were observed. An ELBW infant (G.A. 25 wks, B.W. 810 g) with persistent candidemia, initially unsuccessfully treated with amphotericin B changed to ABLC (owing to reduced urine output and elevated creatinine) and then with fluconazole, responded to therapy with caspofungin and improved renal
function [70]. Another ELBW infant (G.A. 27 wks, B.W. 980 g), who developed *Candida parapsilosis* septicaemia and was resistant to both amphotericin B and fluconazole, was treated with caspofungin for 21 days: the infection was eradicated and renal function tests were normal [71]. Two term newborns with persistent candidemia, unresponsive to catheter removal and amphotericin B treatment, received in addition caspofungin that resulted well tolerated [72]. Odio et al. [73] reported 10 candidemic newborns (1 term, 9 preterm) treated with caspofungin after failure of therapy with amphotericin B: renal function tests did not show any value above normal. Some authors [74] analyzed the use of caspofungin in 13 critically ill neonates (12 preterm and one term) with documented candidemia who failed to respond to conventional antifungal therapy with amphotericin B and/or fluconazole or flucytosine: transient hypokalemia was observed in two patients. Eighteen newborns and infants (< 3 months of age), previously treated with intravenous amphotericin B for highly suspected or documented candidiasis, received multiple once-daily doses of caspofungin as a 1-h infusion. Even if one or more clinical and laboratory adverse events were observed in 94.4% of patients, none resulted drug-related but rather were consistent with prematurity and/or other birth complications [75].

As regards the other echinocandins, relatively few studies report safety data in newborns Among a substudy population of 52 paediatric patients with invasive candidiasis (comprising 7 preterm infants and 14 subjects < 2 years), three cases of hypokalemia were observed and two patients experienced drug discontinuation due to respectively an increase in serum creatinine levels and a worsening of renal failure (76). A total of 18 premature infants (B.W. > 1000g) and 5 preterm weighting 500g to 1000g with infections caused by *Candida* spp were treated with micafungin: a moderate but persistent hypokalemia possibly related to the study drug was observed in one patient [77]. Micafungin was added to other antifungal drugs for the treatment of cutaneous aspergillosis in a premature infant (G.A. 24 wks, B.W. 651 g). The only adverse event possibly related to micafungin was hypokalemia [78]. Recently, in 4 premature infants (mean G.A. 24 wks, mean B.W. 579 g), diagnosed with Candida infections and previously treated with fluconazole, after receiving micafungin no apparent side-effects drug-related have been observed [79].

### 5. Nonsteroidal Antiinflammatory Drugs (NSAIDS)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used in the neonatal period to favour closure of patent ductus arteriosus (PDA) and to reduce polyuria in subjects with congenital salt-losing tubulopathies [80]. The nephrotoxic effects of NSAIDs are related to their mechanism of action: through the block of prostaglandin synthesis with the inhibition of cyclooxygenase (COX) enzymes, these drugs may provoke renal damage that may result in acute renal failure with or without oliguria, chronic renal failure, relevant proteinuria, fluid metabolism alterations and hyperkalemia. Two of the COX isoforms, COX-1 and COX-2 have been widely acknowledged, displaying a similar structure differing by a mere single amino-acid group. However, the site of action, selectivity, and intracellular localization of the two isoforms are quite distinct. COX-1 or the “constitutive” isoform is ubiquitous and constitutively expressed in all tissues under basal conditions, being implicated in the maintenance of normal physiological functions in numerous organs, e.g. stomach and kidney. COX-2 has been termed “inducible” in view of its more restricted expression and upregulation during inflammation. It is undetectable in most mammalian tissues, although expression can be rapidly induced in fibroblasts, endothelial cells, macrophages, synovial tissue, chondrocytes, osteoblasts and ovarian follicles by different inflammatory stimuli including cytokines, endotoxins, hypoxia and growth factors. Identification of the two isoforms has given rise to the so-called “COX hypothesis: COX-1-derived prostaglandins should be involved in regulating physiological functions, whereas COX-2 derived prostaglandins should play a major role during inflammation or tissue damage [81].

At birth, many organ systems undergo important processes of adaptation to extrauterine life. Prostaglandins play a prominent role in postnatal cardiovascular adaptation in general, and particularly in renal adaptation both in normal [82] and in pathological newborns [83]. The perinatal kidney may be deemed as being under permanent stress owing to the high preglomerular and postglomerular vascular resistances. After birth, prostaglandin-induced vasodilation at afferent arterioles, in combination with persistent vasoconstriction at efferent arterioles under the control of the renin-angiotensin
system, modifies glomerular filtration pressure, thus contributing towards a postnatal increase of glomerular filtration rate (GFR) [81,84]. The immature kidney would appear to be programmed especially depending on glomerular and tubular actions of prostaglandins in the perinatal and neonatal period [85]. Interestingly, urinary excretion of PGE2 and PG12 in preterm infants has been found to be 5-fold higher than that observed in term infants, and 20-fold higher than in subjects over the age of 1 month, thereby supporting the concept that renal prostaglandin activity is inversely related to gestational age [81].

For many years indomethacin has been the drug of choice in the treatment and prophylaxis of PDA in premature neonates. Among its side-effects, transient or permanent alterations in renal function have been frequently reported [86]. Reduction of urinary volume and glomerular filtrate usually are reversible within 48 h by discontinuation of therapy, while oliguria may persist for two weeks. Strategies to minimize the renal side-effects of indomethacin such as its association with furosemide or with low doses of dopamine or the use of prolonged low doses have not been successful. In every case, indomethacin seems to have no major long-term renal effects, since some authors showed that kidney function was restored after one month following acute renal impairment.

Ibuprofen has been shown to close successfully the ductus arteriosus in animals and newborns without affecting renal hemodynamics. In a prospective randomised study considering the effectiveness and the side-effects of ibuprofen and indomethacin in the treatment of PDA, observed a marked influence of indomethacin on serum creatinine. In another randomized trial involving five NICUs in Belgium, some authors confirmed that ibuprofen was significantly less likely to induce oliguria and to increase serum creatinine, as also observed by other authors after intravenous and oral administration. In conclusion no statistically significant difference in the effectiveness of ibuprofen compared to indomethacin in closing a PDA was found, but ibuprofen is associated with lower nephrotoxicity.

Numerous issues pertaining to the use of these drugs in neonatology remain. Very recently a whole congress has been devoted to this topic [87], presenting also a research on the actual use on NSAIDs in European newborns [88].

Administration of an unvaried dose of indomethacin or ibuprofen to the newborn despite gestational and/or postnatal age is a paradox, overlooking displayed specific clearance rates based on the age of the infants.

The influence produced by genetic polymorphism on the metabolism of these drugs has been well documented, revealing the presence of Extensive Metabolisers: EM; and Poor Metabolisers: PM) [90]. Ibuprofen compared with indomethacin reduces the risk of oliguria and is associated with lower serum creatinine levels following treatment [91]. However, if toxicity is detected with urinary biomarkers considered early indicators of nephrotoxicity, such as prostaglandins E2, a dramatic decrease in urinary prostaglandins E2 during ibuprofen treatment is observed. In fact, studies performed on both animals (neonatal piglets) and humans (preterm infants with PDA) have shown a reduction in urinary excretion of PGE2 following indomethacin administration. We reported a significant decrease in urinary PGE2 levels following ibuprofen treatment in preterm infants with PDA, revealing a dramatic fall in PGE2 in infants developing significant side effects (intraventricular hemorrhage, acute renal failure, and intestinal perforation) [92].

The role of prostaglandins E2 should be given due consideration in all situations in which the balance between vasoconstrictors (aggressive) and vasodilators (vasoprotective) is essential for the neonatal kidney.

New strategies regarding a tailored dosage of ibuprofen in the first week of life to optimize the dosage, reaching an optimal peak level and abvoiding toxicities, have been proposed [93]. However further studies are needed to confirm this approach [81,92,94].

### 6. Prevention

It is important for the neonatologist to recognize the problem of drug-induced disease because the causative agents are commonly prescribed, nephrotoxicity is frequent and reversible in many patients [1,95].

Thus vigilance and early diagnosis are essential for the management. The most important first step in treating drug-induced nephropaty is to stop the offending drug. This resolves many cases of prerenal, intrinsic and obstructive renal failure. Thus, preventing iatrogenic drug-induced nephrotoxicity is not only possible and desirable, but strictly mandatory. How can one avoid...
nephrotoxicity? In Tab. 1 ten practical rules are presented for prevention. Of particular importance in clinical practice. Finally maximal caution should be used in employing new drugs in paediatrics (unlicensed ad/or off-label) [96].

### Tab. 1

Ten rules for prevention of drug-induced renal damage in the newborn and infant

1. Don’t use nephrotoxic drugs, if alternatives
2. Don’t use nephrotoxic drugs in high risk neonates
3. Choose the less nephrotoxic compound
4. Use correct dosage and therapeutic drug monitoring, if required
5. Don’t use concomitant nephrotoxic drugs, if possible
6. Limit the duration of treatment
7. Perform an early diagnosis of renal damage
8. Stop the administration of the drug, if damage
9. Caution in using new drugs in neonatology (unlicensed and/or off-label)
10. Modify dose and/or interval dosing in renal failure

### References


Dufful SB, Begg EJ. Vancomycin toxicity. What is the evidence for dose dependency? Adverse Drug Reactions and Toxicological Reviews, 13, 2, 1994, 103-114.


[76] Queiroz-Telles F, Berezin E, Leverger G, Freire A, van der Vyver A, Chotpitayasunondh T, Konja J, Diekmann-


