Therapeutic Dilemma

Is NSAID use in children associated with the risk of renal injury?

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Abstract

Renal injury is known to be a risk of nonsteroidal anti-inflammatory drug (NSAID) therapy in adults. While this appears to be much less common in children, there are some groups of children who do appear to be at risk of renal injury associated with NSAID therapy and clinicians caring for these patients need to be cognizant of this potential risk.

Keywords: *Children; Drug safety; NSAIDs; Renal injury.*

THE THERAPEUTIC DILEMMA

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs worldwide. Indications for use in paediatrics vary based on age with tocolysis and patent ductus arteriosus (PDA) closure being common reasons for exposure in the fetus and neonate, and pain, fever, and swelling being indications for use in older children and adolescents. NSAIDs have been shown to have numerous adverse effects, including nephrotoxicity. While this has been extensively studied and analyzed in adults, the clinical significance of this toxicity has not yet been well delineated in paediatrics.

BACKGROUND

NSAIDs act by disrupting prostaglandin synthesis through inhibition of the cyclooxygenase (COX) enzymes. In a euvoletic state, prostaglandin inhibition may not have a clinically significant impact on the hemodynamic status of the kidney. In a state of volume contraction, the renin-angiotensin-aldosterone system acts to induce vasoconstriction and renal prostaglandin synthesis. These prostaglandins act to cause vasodilation of the afferent arteriole, thus maintaining renal perfusion during such states. Inhibition of prostaglandin biosynthesis by NSAIDs in this state may compromise this protective effect (1).

Acute kidney injury (AKI) is abrupt loss of renal function with a decline in glomerular filtration rate. The mechanism underlying this condition is typically classified as prerenal

(hypoperfusion to the kidney), intrinsic renal (vascular, glomerular, tubular, interstitial), or postrenal (obstruction). NSAID-induced nephrotoxicity generally involves the prerenal or intrinsic pathology; most notably acute tubular necrosis (ATN) wherein ischemia or toxins result in the death of tubular epithelial cells, and acute interstitial nephritis (AIN) wherein a reaction to drugs or infection results in inflammation of the interstitial tissue (1). It is increasingly recognized that even a single episode of AKI substantially increases the long-term risk of chronic renal injury.

The most commonly reported clinical features of NSAID-induced nephrotoxicity in the paediatric population include oliguria or anuria. The most noteworthy laboratory finding is an elevated serum creatinine level (1). In children, other features include hypertension and proteinuria, which can persist after normalization of serum creatinine while another indication of renal injury can be hyperfiltration with supranormal renal function (1).

NEPHROTOXICITY IN THE FETUS

All medications should be used with caution during pregnancy, and NSAIDs are no different. This class has, however, been used for years in pregnant women, most notably as tocolytic agents to prevent premature delivery. There are a number of adverse events to ibuprofen in the neonate associated with maternal NSAID use including renal failure and anuria. While the

incidence of reported renal impairment in such cases are relatively rare given the widespread use of NSAIDs in this population, there are a number of case reports of varying degrees of nephrotoxicity in fetuses of mothers who used NSAIDs during pregnancy (most commonly indomethacin). Musu et al. conducted an analysis of seven case reports identifying 153 babies with a history of in-utero exposure to NSAIDs. Within these groups, numerous renal adverse effects were identified and attributed to NSAIDs, most notably: renal failure, fatal anuria, oliguria, and increased creatinine (2).

In addition to the functional impairment attributed to NSAIDs, structural changes to the kidney have been reported in newborns with in-utero exposure to this class prior to the completion of nephrogenesis at 36 weeks. It is hypothesized that prostaglandins play a pivotal role in the development of the kidney, and COX inhibition during this process may result in irreversible changes in the glomerulus and tubules (3). While the risk of structural renal impairment due to NSAIDs may never be eliminated altogether, it appears to be significantly lower when exposure occurs after nephrogenesis has completed (3).

From the available literature on fetal renal dysfunction due to maternal NSAIDs, a number of risk factors have been identified: multiple pregnancies, prolonged and cumulative doses, short timeframe between administration and delivery, genetic factors, low birth weight, and concomitant nephrotoxic drugs (aminoglycosides, glycopeptides, and diuretics) (2).

NEPHROTOXICITY IN THE NEWBORN

In the neonatal period, NSAIDs are commonly used for closure of the patent ductus arteriosus. Their administration may be prophylactic, or used as early or late treatment. Indomethacin was the first agent of choice for PDA closure, but has been associated with both acute and long-term nephrotoxicity, resulting in ibuprofen gaining popularity as the first-line option. A group in Italy, Fanos et al. conducted an analysis of the major randomized controlled trials comparing indomethacin and ibuprofen for PDA closure. The group reported that both drugs had equivalent efficacy, but that ibuprofen was associated with less nephrotoxicity. In comparison to indomethacin, ibuprofen was determined to be less likely to cause oliguria, or increased serum creatinine in neonates with both intravenous and oral administration. With regards to the differing levels of nephrotoxicity among drugs of the NSAID family, the authors offer three possible explanations, each of which may play a role:

- 1) Different NSAIDs inhibit COX enzymes to varying extents
- 2) The diverse pharmacokinetics of different NSAIDs may dictate their potential to impair renal function
- 3) Nonprostaglandin effects may play a role in the nephrotoxicity of these drugs (4)

NEPHROTOXICITY IN CHILDREN AND ADOLESCENTS

There are indications NSAIDs in children and adolescents are similar to in adults; they are used primarily for their analgesic, antipyretic, and anti-inflammatory properties. Reports of NSAID-associated renal failure in otherwise healthy children are rare. A randomized control trial of 83,915 outpatient children with fevers reported no increased risk of renal failure in the 55,785 patients who received short-term ibuprofen versus the acetaminophen control group (1). However, hospitalized children are very commonly given NSAIDs and may be at higher risk of nephrotoxicity.

A retrospective study conducted at Indiana University Health analyzed paediatric cases of AKI 1999 through 2010 to determine how many of these could be attributed to NSAIDs (5). From the 1015 AKI cases, 27 (2.7%) were judged to be NSAID-related AKI. Twenty-one of the 27 cases had ATN and the other 6 had AIN. Of note, the authors contend that this may be an underestimate as cases of AKI that were felt to be multifactorial (including those in which NSAIDs may have contributed) were excluded. The authors note that the majority of NSAID-associated AKI cases occurred with patients taking the recommended dose of the drug. The authors also provided an analysis of 54 other patients with a variety of conditions presented in case reports between 1993 and 2009 wherein they identify that after discontinuation of the offending NSAID, most patients would eventually go on to recover their renal function (5). A very large trial of more than 84,192 children comparing acetaminophen to ibuprofen demonstrated that there did not appear to be an increased risk of renal failure following short-term use of ibuprofen in children, but was unable to comment on more prolonged use or use in special circumstances (6). While a study of high-dose ibuprofen in children with cystic fibrosis (CF) did not demonstrate evidence of renal injury as assessed by urinary biomarkers, a short case series has suggested that NSAID use in volume-depleted children with serious illness is associated with an increased risk of renal injury (7,8).

With varying results from both the outpatient and inpatient setting it is difficult to delineate the overall nephrotoxic risk of NSAIDs in children. There are however, certain risk factors for NSAID-induced AKI identified by Musu et al. and others including: factors that decreased intravascular volume such as dehydration, low protein states such as liver failure, factors that impact perfusion such as congestive heart failure, liver failure, cystic fibrosis, urinary tract or renal problems, recurrent urinary tract infections, NSAID multitherapy, and concomitant drug (beta-blockers, aminoglycosides, ACE inhibitors, diuretics) and alcohol use (2,9–12).

CONCLUSION

NSAIDs are the most widely used drug class in the world, and are used in every age group. Their advantages and drawbacks vary with

the age of the patient. In pregnancy, as with all medications, care should be taken with NSAID use. Particular caution should be taken by mothers who possess identified risk factors for NSAID-induced nephrotoxicity, and avoidance of NSAIDs during nephrogenesis (up to 36 weeks) is recommended if possible. However, the risk-benefit analysis should remain an integral part of the therapeutic conversation between physicians and pregnant patients.

In neonates with patent ductus arteriosus, current literature suggests that ibuprofen should be considered as the first-line medical therapy due to its favourable renal outcomes compared to indomethacin. It should be remembered that renal failure in neonates can be polyuric and renal function should be evaluated by more than measurement of urine output prior to administration of an NSAID in a very ill neonate. In older children and adolescents who are otherwise healthy, NSAID-induced AKI appears to be rare; however, physicians should be cautious of patients with risk factors for NSAID-induced nephrotoxicity, notably pre-existing volume contraction. When managing hospitalized patients in this age group, NSAIDs may best be avoided, or if this is not possible, ensuring that patients are euvolemic and monitoring for oliguria or anuria should be part of the care plan, as early withdrawal of the offending agent may allow for recovery of renal function. Pursuant to this, given that ibuprofen use is often for symptomatic treatment of fever and that fever in this context is usually benign and may be beneficial, a greater tolerance of fever could be associated with less use of NSAIDs.

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