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Ibuprofen-associated Renal Toxicity in Children **Marcia L. Buck, Pharm.D., FCCP**

Since its release in a suspension dosage formulation, ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), has rapidly become a mainstay in the management of pain and fever in children. Originally available only with a prescription, ibuprofen was approved for over-the-counter (OTC) sales in 1984 in adults and in 1995 for children. In most children, ibuprofen is well tolerated^{1,2} and does not produce significant adverse effects, even in moderate overdoses.³ An increasing number of cases of renal toxicity associated with ibuprofen use, however, have caused many practitioners to question our widespread use of this drug.

Mechanism of Injury

There are three ways by which NSAIDs can adversely affect renal function.⁴⁻⁶ The most commonly seen effect is a reduction in renal prostaglandins resulting from inhibition of the cyclooxygenase pathway. In normal subjects, prostaglandins play only a minor role in maintaining renal blood flow and glomerular filtration rate. Under conditions of dehydration and volume constriction, however, renal prostaglandins such as PGE₂ and prostacyclin (PGI₂) become a major factor in maintaining renal blood flow by acting as direct vasodilators and stimulating renin release. The reduction in renal prostaglandins caused by NSAID use alters this balance and may result in electrolyte imbalance, renal hypoperfusion, and acute tubular necrosis or cortical necrosis. In most cases, these changes are reversible.

Other types of NSAID-induced renal injury may not be reversible. A second mechanism involves a hypersensitivity response to NSAIDs that can be seen as interstitial nephritis, nephrotic syndrome, or minimal change glomerulonephritis. A third proposed mechanism is direct cytotoxic injury by NSAIDs and their metabolites resulting in interstitial nephritis and papillary necrosis. Ibuprofen has been linked with each of these types of injury.

While the relative propensity of NSAIDs to cause renal dysfunction has not been well established, ibuprofen appears to be one of the more nephrotoxic among the class. In a study of 12 women with asymptomatic, mild renal failure who were given ibuprofen, piroxicam, and sulindac in a cross-over comparison, three had significant elevations of serum creatinine and potassium within 8 days of starting ibuprofen. None of the patients had toxic symptoms while on piroxicam or sulindac during the full 11 day treatment period.⁵

Reports in Children

In 1989, van Biljon reported a case of reversible renal failure in a 10 year old boy given ibuprofen.⁴ The previously healthy child had been admitted to a local hospital following traumatic injury. He was given ibuprofen 200 mg every 8 hours for headaches and pain. Five days after admission, he became edematous, oliguric, and exhibited signs of confusion. On the sixth day, he had a tonic-clonic seizure and was transferred to a regional institution. On admission, he was comatose and hypertensive, with clear signs of acute renal failure. Ibuprofen use was not continued. Supportive care was initiated, and the patient recovered complete renal function over the following 2 weeks. The authors suggested that the initial blood loss following the patient's injury, coupled with chronic ibuprofen administration, led to the development of acute renal failure.

McIntire and coworkers reported another two patients with NSAID-induced renal dysfunction in 1993.⁷ Both healthy adolescents developed flank pain and progressed to nonoliguric renal failure, one after flurbiprofen (100 mg every 12 hours for 2 days) and one after ibuprofen use (200 mg every 6 hours for 3 days). They recovered full renal function within a week of stopping NSAID therapy. In a letter to the editor in response to McIntire's report, Wattad and

colleagues reported a 14 year old girl with a similar presentation.⁸ The patient had taken a single 600 mg dose of ibuprofen for menstrual pain approximately one week before the onset of flank pain. While a urinary tract infection was being ruled out, BUN and serum creatinine were found to be elevated (43 mg/dl and 4.7 mg/dl, respectively). As in one of the previous cases, biopsy showed mild interstitial nephritis without fibrosis. The patient recovered within 3 weeks.

Another case of ibuprofen-associated acute renal failure was reported by Primack and colleagues in 1997.⁹ In this report, an 11 year old boy who was taking amoxicillin and ibuprofen over a 12 day period for sinusitis developed increasing weakness and vomiting. The ibuprofen dose administered was 200 mg (3 mg/kg) every 8 hours. Upon admission, serum creatinine was 3.7 mg/dl, and potassium was 7.6 mg/dl. Renal biopsy on the third day of admission revealed interstitial infiltration with non-caseating granulomas surrounding necrotic tubules. With supportive care, renal function slowly improved. Within 6 weeks, the patient had recovered clinically, but renal function indices did not return to baseline values for 4 months.

Moghal, Hulton, and Milford reported an additional three cases of ibuprofen toxicity in children.¹⁰ In the first case, a 5 year old boy who had received an earlier renal transplant was admitted for a viral infection. His chronic medication regimen included cyclosporine, azathioprine, and prednisolone. When the patient's fever failed to respond to acetaminophen, a single 5 mg/kg dose of ibuprofen was given. The following day, the patient became anuric for a period of 14 hours and serum creatinine doubled. With close monitoring, the patient recovered within 5 days.

In the second case, a 6.5 year old with a pleural effusion was given ibuprofen 100 mg every 6 hours (20 mg/kg/day) in addition to acetaminophen for fevers. He was moderately dehydrated and developed a gradual increase in serum creatinine. Renal function continued to deteriorate over the next several days and a biopsy revealed acute tubular necrosis. It is presumed that the patient had a poststreptococcal glomerulopathy worsened temporarily by ibuprofen use. In the third case, a 7.5 year old girl with hyper-IgE syndrome and pneumonia was given a single 100 mg (5 mg/kg) dose of ibuprofen in the emergency department. She was vomiting and moderately dehydrated at the time.

On admission to the hospital the following day, she was anuric and required rehydration and eventually hemodialysis. Renal biopsy revealed cortical and tubular necrosis. The patient was left with chronic renal failure.

Nephrotoxic medications, such as the cyclosporine described in the earlier case, can worsen the effect of ibuprofen on the kidney. Four cases of transient renal failure have been reported in children with cystic fibrosis who were receiving chronic ibuprofen and being treated with aminoglycosides for pulmonary exacerbations.¹¹ The patients included a 16 year old girl, a 10 year old girl, and twin 23 month old boys. In all four cases, chronic ibuprofen was continued on admission, when tobramycin or gentamicin was initiated.

The 16 year old patient in this case series developed peripheral edema and oliguria after one day of ibuprofen use, with an increase in serum creatinine to 2.8 mg/dl. She died 9 days later of her underlying disease; autopsy revealed interstitial nephritis. The 10 year old girl experienced nausea, vomiting, and abdominal cramps two days after admission. Her serum creatinine rose from 0.7 mg/dl to 2.4 mg/dl during that time. Both her ibuprofen and gentamicin were discontinued, and renal function recovered within 5 days. The twins were admitted at the same time. One twin developed lethargy, vomiting, and edema after 9 days of both ibuprofen and gentamicin. His serum creatinine rose from 0.2 to 5.2 mg/dl; he required peritoneal dialysis until renal function recovered. His brother had a transient, asymptomatic increase in serum creatinine from 0.4 to 1.5 mg/dl. The authors recommended that ibuprofen therapy be discontinued in any child with cystic fibrosis requiring aminoglycosides.

Several case reports have also documented acute renal failure after a single, large overdose. In 1995, Kim and colleagues reported a case of acute renal insufficiency in an otherwise healthy 2 year old boy.¹² He had ingested approximately 40 ibuprofen 200 mg tablets (approximately 640 mg/kg). On arrival to an emergency department 4 hours after the ingestion, he was lethargic and tachycardic. Metabolic acidosis was noted, but BUN and serum creatinine were within normal limits. Despite charcoal and fluid administration, the patient progressed to acute nonoliguric renal insufficiency within 12 hours. Serum creatinine rose from 0.46 to 2.1 mg/dl at hour 27. With continued supportive therapy, renal function

recovered rapidly, returning to baseline values at 72 hours.

Al-Harbi, Domrongkitchaiporn, and Lirenman reported a similar case in 1997.¹³ A 21 month old boy ingested approximately 8 grams of ibuprofen (500 mg/kg) and developed acute renal failure with metabolic acidosis. The patient progressed to tonic-clonic seizures on the second day after the ingestion, likely the result of severe hypocalcemia and hypomagnesemia. Serum creatinine increased from a level of 0.6 mg/dl 2 hours after admission to a maximum of 2.5 mg/dl at 34 hours. With supportive care, including fluids and electrolyte replacement, the patient recovered within a week.

Assessing the Risk

The case reports presented here demonstrate the variety of situations in which ibuprofen-associated renal toxicity can occur. In many of the cases, the children were already at risk for renal adverse effects because of underlying disease states, concomitant medications, or dehydration. While the focus of this issue is to make health care providers aware of the risks associated with ibuprofen, it is important to put these risks into proper perspective.

Lesko and Mitchell have attempted to identify the degree of risk associated with ibuprofen use in children. In 1995, they reported the results of a large randomized, double-blind trial comparing ibuprofen with acetaminophen.¹ Children with febrile illnesses were assigned to either 12 mg/kg acetaminophen or ibuprofen at a dose of either 5 or 10 mg/kg throughout their illness. Renal function at baseline, as measured by BUN and serum creatinine values, was not significantly different among the groups. In this study, the authors focused on the frequency of severe adverse effects with both drugs. No patients in any of the three treatment groups developed acute renal failure. There were also no differences in the incidence of gastrointestinal bleeds or anaphylaxis.

In 1997, these same authors set out to test the hypothesis that short-term ibuprofen use increases the risk of renal impairment in children as measured by BUN and serum creatinine.¹⁴ Using the data from their original study, they reviewed the cases of 288 children who were hospitalized and had laboratory studies available. A median number of seven doses of the antipyretics were taken by the patients; the range was not reported. During hospitalization, BUN

and creatinine values did not differ among the groups. The prevalence of elevated values was also no different. Based on these results, the authors concluded that short-term ibuprofen use was unlikely to cause renal toxicity.

Methods for Prevention

In order to prevent ibuprofen-associated renal toxicity, the patients at greatest risk must be identified. Children with renal insufficiency, congestive heart failure, or hepatic dysfunction are known to be at increased risk. Children receiving other nephrotoxic drugs, such as cyclosporine or aminoglycosides, or those receiving drugs which alter or are affected by changes in serum potassium concentrations, such as spironolactone, digoxin, or potassium supplements, may also be at risk. These patients should be given ibuprofen only under the guidance of a health care provider.

Otherwise healthy children may be given ibuprofen in appropriate doses, 5 to 10 mg/kg every 6 to 8 hours, for short periods. It is recommended that children be given ibuprofen for no more than 3 days without the supervision of a health care provider. As with acetaminophen, caregivers should be instructed to calculate and measure doses carefully and to look for the generic name in all OTC products, to avoid giving more than one ibuprofen-containing product simultaneously.

Caregivers should also understand the signs of dehydration and the importance of avoiding ibuprofen during illnesses accompanied by vomiting, decreased fluid intake, or diarrhea. If ibuprofen-associated renal toxicity is suspected, by decreased urine output, weakness, or fatigue, prompt medical attention is needed.

Summary

In most patients, ibuprofen is a safe and effective antipyretic and analgesic. One known adverse effect of therapy is renal dysfunction. Children with underlying illnesses or those who receive ibuprofen for a prolonged period while dehydrated are at greatest risk for this injury. Caregivers should be aware of this possibility and limit ibuprofen use appropriately.

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Literature Review

Cefuroxime during pregnancy

The authors of this paper present the results of a retrospective analysis of 78 women who received oral cefuroxime axetil during pregnancy. Thirteen of the women were treated in the first trimester, 19 in the second, and 46 in the third. The majority were treated for urinary tract infections. Eighty children were born to these women. The children were monitored for 18 months after birth. No abnormalities were noted, suggesting that oral cefuroxime is a safe antibiotic alternative during pregnancy. Manka W, Solowiow R, Okrzeja D. Assessment of infant development during an 18-month follow-up after treatment of infections in pregnant women with cefuroxime axetil. **Drug Safety** 2000;22:83-8.

Herbal therapy review

With the increasing popularity of herbal therapies in the United States, this basic reference will be a useful addition to the files of any health care provider. The authors give basic information about a variety of commonly used herbal products, as well as a discussion of the regulatory processes that govern sales and

marketing of these products. The appendix provides a brief list of additional resources that may be of interest. Boullata JI, Nace AM. Safety issues with herbal medicine. **Pharmacotherapy** 2000;20:257-69.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 3/24/00:

1. Inhaled nitric oxide (INOMax[®]) was added to the Formulary, restricted to its approved indication for the management of persistent pulmonary hypertension in neonates.

2. Transdermal lidocaine (Lidoderm[®]) was also added to the Formulary. This product is restricted to the Pain Service for a 6 month trial.

3. Iopanoic acid (Telepaque[®]) was added for use in cholecystography and the management of acute hyperthyroidism.

4. Levonorgestrel (Plan B[®]), an emergency contraceptive, was also added the Formulary.

5. Cisapride (Propulsid[®]) was removed from the Formulary pending voluntary removal of the drug from the market by the manufacturer on July 14, 2000. This action was prompted by the accumulation of 341 reports of arrhythmias and 80 patient deaths linked to cisapride use. For more information, see the FDA website at <http://www.fda.gov/bbs/topics/answers/ans01007.html>

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