NSAID Nephrotoxicity Revisited: Selective COX-2 Inhibitors

December 31, 2006
By Kory Tray, MD [1] and Mark A. Perazella, MD [2]

For over 25 years, NSAIDs have been used to treat a variety of pain syndromes and inflammatory diseases. More than 50 million Americans take these drugs. Unfortunately, control of pain and inflammation is not achieved without an associated cost—namely, GI complications and, to a lesser extent, nephrotoxicity. In an attempt to reduce drug-related toxicity, a new class of selective NSAIDs—the COX-2 inhibitors—was introduced in 1999. These selective NSAIDs are as effective as and pose less risk of gastric toxicity than nonselective NSAIDs.1,2 The COX-2 inhibitors are thought to reduce end-organ injury, such as GI ulceration, by sparing homeostatic or “constitutive” COX-1 enzyme function.1,2 In contrast, therapeutic effects result from the inhibition of the “inducible” COX-2 enzyme.1,2 Such drug effects target the production of proinflammatory prostaglandins by COX-2 without interrupting normal cell function mediated by COX-1.2,3

Q: How safe are the cyclooxygenase-2 (COX-2) inhibitors for patients at risk for NSAID nephrotoxicity? A: For over 25 years, NSAIDs have been used to treat a variety of pain syndromes and inflammatory diseases. More than 50 million Americans take these drugs. Unfortunately, control of pain and inflammation is not achieved without an associated cost—namely, GI complications and, to a lesser extent, nephrotoxicity. In an attempt to reduce drug-related toxicity, a new class of selective NSAIDs—the COX-2 inhibitors—was introduced in 1999. These selective NSAIDs are as effective as and pose less risk of gastric toxicity than nonselective NSAIDs.1,2 The COX-2 inhibitors are thought to reduce end-organ injury, such as GI ulceration, by sparing homeostatic or “constitutive” COX-1 enzyme function.1,2 In contrast, therapeutic effects result from the inhibition of the “inducible” COX-2 enzyme.1,2 Such drug effects target the production of proinflammatory prostaglandins by COX-2 without interrupting normal cell function mediated by COX-1.2,3

PROSTAGLANDINS AND RENAL FUNCTION Prostaglandins are the major products of COX enzyme metabolism. These prostanooids are produced throughout the body and act locally in an autocrine and/or paracrine fashion. Following synthesis, prostaglandins promptly exit the cell via facilitated diffusion to bind to prostaglandin receptors found on parent or neighboring cells, thereby modulating cellular functions.4 In healthy persons, prostaglandins are not the primary regulators of kidney function. Rather, these eicosanoids locally modulate the effects of vasoconstrictor hormones.5 The major prostaglandins synthesized in the kidney include PGIl, PGE2, thromboxane A2 (TXA2), and PGF2α (Table 1). These prostaglandins are produced to preserve renal function when pathologic states supervene and compromise physiologic kidney processes. Intravascular volume depletion—associated with vomiting, diarrhea, and diuretic therapy—stimulates COX enzyme activity and prostaglandin synthesis to optimize renal blood flow.6 Other causes of an effective decrease in renal blood flow include congestive heart failure (CHF), cirrhosis, and nephrotic syndrome. Prostaglandin production is also increased in chronic renal insufficiency to maintain perfusion of remnant nephrons.7 Locally produced PGIl and PGE2 antagonize the local effects of circulating angiotensin II, endothelin, vasopressin, and catecholamines that normally maintain systemic blood pressure at the expense of the renal circulation.8 Glomerular filtration rate (GFR) is preserved through the antagonism of arteriolar vasoconstriction and mesangial and podocyte contraction, both of which are induced by endogenous vasoressors.4,8–10 Renal prostaglandins also have an important role in modulating salt and water homeostasis. In states of volume overload, both the inhibition of tubular sodium chloride reabsorption and the impairment of vasopressin's effect on water channels result in increased salt and water excretion.5,8 Regulation of medullary blood flow by PGE2 also contributes to the kidney's ability to modify renal solute excretion.5,8 Ultimately, intravascular volume status is controlled, and hypotension and dehydration—as well as hypertension and edema formation— are avoided. NSAID-ASSOCIATED NEPHROTOXICITY Patients with high-renin states (such as CHF, volume depletion, and cirrhosis) and chronic renal insufficiency rely on renal prostaglandin synthesis to ensure sufficient renal blood flow and to maintain an adequate GFR. In the absence of these prostaglandin effects, unopposed vasoconstriction leads to a decrease in renal blood flow and a decline in GFR.5,8 Thus, NSAID therapy in patients with prostaglandin-dependent disease states often precipitates renal ischemia and acute renal failure.5,8 Fortunately,
discontinuation of the NSAID leads to reversal of renal failure within 2 to 5 days. In some cases, short-term dialysis may be required for severe uremia or extreme metabolic perturbations. Edema formation and volume overload may also complicate NSAID therapy. In elderly patients with underlying heart disease, NSAID use can double the risk of CHF. Diuretic resistance can also develop during NSAID therapy, especially in patients with underlying salt-retentive states, such as CHF and cirrhosis. In addition, new-onset hypertension and exacerbation of previously well-controlled hypertension can occur with NSAIDs. Most of these adverse effects result predominantly from NSAID-induced sodium retention by the kidney. NSAIDs also potentiate the antidiuretic effects of vasopressin, which can lead to total body water excess and hyponatremia. Severe and potentially life-threatening hyperkalemia can develop following NSAID therapy. This most often occurs in patients with underlying renal insufficiency or in those who are concurrently receiving other medications that alter potassium balance. An NSAID-induced reduction in the synthesis of renin and aldosterone is the major cause of impaired renal potassium excretion and hyperkalemia. Decreased delivery of sodium chloride and water to the distal nephron, which is perpetuated by the effect of the NSAID, also contributes to the development of hyperkalemia. The diminished availability of intraluminal sodium for sodium-potassium exchange limits potassium excretion.

**EFFECT OF COX-2 INHIBITORS ON RENAL FUNCTION** Clinical data on the effect of selective COX-2 inhibitors on renal function are limited to a small number of clinical trials and a handful of reported cases. Four studies provide preliminary insight into the potential nephrotoxicity of these drugs. In general, the participants were healthy and maintained relatively well-preserved renal function during the study. Thus, these patients were at low risk for nephrotoxicity, and the results of these trials should not be extrapolated to patients with prostaglandin-dependent states (eg, CHF, cirrhosis, use of diuretics) or severely impaired renal function. In addition, the 4 studies examined only the short-term effects of COX-2 inhibitors on renal function. In these trials, which studied celecoxib and rofecoxib, the effects of the COX-2 inhibitors can be summarized as follows.

- Significantly decreased renal prostaglandin synthesis in all studies in which this was measured.
- Significantly reduced renal sodium excretion regardless of whether an ad-lib or sodium-restricted diet was used.
- Reduced GFR only in patients in whom salt intake was restricted. The GFR was well maintained in patients treated with COX-2 inhibitors who did not follow a salt-restricted diet.

Several case reports describe the clinical effects of COX-2 inhibitors on renal function in patients with multiple risk factors for NSAID-induced nephrotoxicity. Three patients experienced acute renal failure and hyperkalemia following therapy with these medications. Discontinuation of the COX-2 inhibitor and treatment of the associated intravascular volume disturbance reversed the renal dysfunction and electrolyte imbalance in these patients. More recently, 2 case series described 10 patients who had acute renal failure and a variety of electrolyte and acid-base disorders following therapy with either celecoxib or rofecoxib. These patients had multiple underlying risk factors for NSAID nephrotoxicity, including diuretic therapy, hypertension, and CHF. All recovered to baseline renal function after the COX-2 inhibitor was discontinued and associated intravascular volume disturbances were corrected.

**IMPLICATIONS FOR YOUR PRACTICE** The available data suggest that COX-2 inhibitors disturb important components of renal physiology. These selective NSAIDs reduced sodium excretion, which suggests that COX-2-synthesized prostaglandins have a major role in the regulation of renal salt and water. Furthermore, salt restriction in patients treated with COX-2 inhibitors, through the induction of volume depletion, was associated with a reduction in GFR. In patients with multiple risk factors for traditional NSAID nephrotoxicity (Table 2), the COX-2 inhibitors induced severe acute renal failure and electrolyte disturbances. Thus, it appears that COX-2 inhibitors, like traditional NSAIDs, impair the physiologic roles of prostaglandins in the kidney. It is therefore prudent to approach therapy with these drugs as you would with traditional NSAIDs in patients at risk for nephrotoxicity.

**REFERENCES:**


Source URL:
http://www.psychiatrictimes.com/articles/nsaid-nephrotoxicity-revisitedselective-cox-2-inhibitors

Links: