Cyclooxygenase-2 Inhibitor–Associated Acute Renal Failure: Case Report with Rofecoxib and Review of the Literature

Enid Morales, Pharm.D., and Jeffrey J. Mucksavage, Pharm.D.

Cyclooxygenase (COX)-2 inhibitors are widely prescribed for their antiinflammatory and analgesic effects. The potential for COX-2 inhibitors to exert deleterious effects on renal function similar to those of traditional nonsteroidal antiinflammatory drugs is not well defined. Until recently, COX-1 was considered responsible for the synthesis of renal prostaglandins. However, COX-2 is also constitutively expressed in the human kidney. Clinical studies have reported a significant decrease in glomerular filtration rate in young and elderly sodium-depleted volunteers given COX-2 inhibitors. We describe the case of a 71-year-old woman who developed acute renal failure after receiving a 50-mg dose of the selective COX-2 inhibitor rofecoxib. (Pharmacotherapy 2002;22(10):1317–1321)

Traditional nonsteroidal antiinflammatory drugs (NSAIDs) inhibit both isoforms of the enzyme cyclooxygenase (COX). The first, COX-1, is constitutively expressed in most cells throughout the body, and its inhibition has been associated with gastrointestinal bleeding and ulceration. In contrast, COX-2 expression is induced in the presence of inflammation and its inhibition results in the therapeutic effects of NSAIDs. Thus, the development of selective COX-2 inhibitors brought about a new way to produce potent antiinflammatory actions with a decreased risk of significant gastrointestinal adverse effects.[1–6]

In addition to the gastrointestinal side effects of NSAIDs,[7, 8] renal toxicity, including acute renal failure, is described in the literature.[9–11] These agents can be particularly harmful to renal function in patients relying on the vasodilatory actions of prostaglandins in the kidney. However, the potential for COX-2 inhibitors to have effects on renal function similar to those of NSAIDs is not well defined, and the role of COX-2 in the human kidney is not fully understood.[12–14] Several in vitro[15–18] and clinical[2–5, 19–22] studies have begun to elucidate the role of this enzyme and the effects of its inhibition on renal function. Case reports of selective COX-2 inhibitor-associated acute renal failure are emerging.[23, 24]

From the Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Rutgers–The State University of New Jersey, Piscataway, New Jersey (Dr. Morales); and the Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois (Dr. Mucksavage).

Address reprint requests to Enid Morales, Pharm.D., BCPS, Rutgers–The State University of New Jersey, Ernest Mario School of Pharmacy, Department of Pharmacy Practice and Administration, 160 Felinghuysen Road, Piscataway, NJ 08854-8020.

Case Report

A 71-year-old Chinese woman came to the emergency department complaining of progressive dyspnea and decreased urine output. She had been in her usual state of health until 3 days before her visit, when she developed left knee pain and swelling. At that time, her primary care physician thought that she was experiencing an episode of gout due to her significant diuretic therapy and prescribed allopurinol 300 mg/day and rofecoxib 50 mg/day. The patient took one dose of both agents 24 hours before coming to the emergency department. For the next 24 hours, she reported a significant decrease in urine output despite taking furosemide 60 mg

twice/day. She was admitted to the hospital for evaluation of acute renal failure.

The patient's medical history was significant for coronary artery bypass graft, mitral valve replacement, and pacemaker placement. She also had a history of hypercholesterolemia and chronic heart failure (with a reported ejection fraction of 20%) after her cardiac surgeries 2 years earlier. The patient's drug therapy consisted of furosemide 60 mg twice/day, metolazone (strength unknown) 0.25 tablet every 4 days, potassium chloride 10 mEq twice/day, losartan 50 mg/day, atenolol 12.5 mg/day, digoxin 0.125 mg/day, atorvastatin 10 mg/day, and warfarin 2.5 mg/day. Besides the addition of rofecoxib and allopurinol, no other changes in her pharmacologic regimen were reported.

At the emergency department, the patient was afebrile, blood pressure was 108/80 mm Hg, pulse 80 beats/minute, and respiratory rate 20 breaths/minute. Physical examination showed no evidence of fluid overload. Mucous membranes were moist. The patient had no jugular venous distention, lungs were clear to auscultation, and no signs of edema were present in the extremities. Electrolytes were within normal limits: serum sodium 136 mEq/L (normal range 136–145 mEq/L), potassium 4.5 mEq/L (3.5–5.0 mEq/L), chloride 100 mEq/L (98–108 mEq/L), and CO_2 26 mEq/L (24–32 mEq/L). Blood urea nitrogen (BUN) and serum creatinine were elevated at 54 mg/dl (6–23 mg/dl) and 2.9 mg/dl (0.5–1.2 mg/dl), respectively. Two months before admission, the patient's BUN and serum creatinine were 27 mg/dl and 1.1 mg/dl, respectively. Complete blood count with differential, creatine kinase, and serum digoxin levels were within normal limits. International normalized ratio was elevated at 7.4 without clinical evidence of bleeding. Urinalysis on admission showed a pH of 5.0, specific gravity 1.015, 2+ protein, 1+ blood, and negative leukocyte esterase, glucose, ketones, and eosinophils. Urine sediment showed few epithelial cells and no casts. Urine sodium concentration was 29 mEq/L. Chest radiograph showed cardiomegaly but no evidence of acute chronic heart failure.

In the emergency department, all drug therapy was held and gentle hydration was started with 5% dextrose-0.9% saline at 75 ml/hour. One day after admission, the patient's BUN and serum creatinine decreased to 40 mg/dl and 1.1 mg/dl, respectively. At that time, renal ultrasound was performed and showed no evidence of hydronephrosis or masses. Two days after admission, BUN and serum creatinine levels returned to the patient's baseline values of 29 mg/dl and 0.9 mg/dl, respectively, and she was discharged.

Discussion

Prostaglandins are necessary to preserve renal hemodynamics in conditions associated with high adrenergic and renin-angiotensin stimulation, such as heart failure, liver failure, and renal insufficiency.[9, 12–14] The vasoconstriction associated with adrenergic and angiotensin activation increases intrarenal release of prostaglandin E_2 (PGE_2) and PGI_2. Renal blood flow and glomerular filtration rate (GFR) are maintained by the opposed vasodilatory effect of these prostaglandins. In addition to their hemodynamic effects, prostaglandins are necessary to sustain salt and water excretion.[9, 12–14] For example, PGE_2 inhibits reabsorption of sodium and chloride and antagonizes antidiuretic hormone. Inhibition of COX-1–mediated prostaglandin synthesis by nonselective NSAIDs therefore can promote salt and water retention and decreased renal function in patients who have chronic heart failure, liver disease, or renal disease, or who are volume or sodium depleted.[9–14]

Until recently, COX-1 was thought to be responsible for the synthesis of renal prostaglandins. Thus, the administration of selective COX-2 inhibitors would avoid the detrimental renal effects of NSAIDs. However, recent evidence no longer supports this notion; COX-2 has been found to be constitutively expressed in the human adult kidney,[18] and sodium restriction induces COX-2 expression in animal models.[15, 16] Although no clear evidence exists as to whether high adrenergic and renin states induce COX-2 expression in the human kidney, recent clinical studies suggest that COX-2 may have an important role in regulating renal perfusion and glomerular hemodynamics.[19–22] Although no difference in GFR has been reported with selective inhibition of COX-2 in healthy, non–sodium-depleted elderly individuals,[19, 20] GFR has been shown to decrease in young and elderly sodium-depleted volunteers.[21, 22] In addition, cases of acute renal failure associated with administration of COX-2 inhibitors have been reported.[23, 24]

The effects of COX-1 and COX-2 inhibition on renal hemodynamics and water balance were examined in 36 healthy elderly volunteers (age range 59–80 yrs).[19] Individuals who had

creatinine clearances less than 50 ml/minute, serum creatinine levels higher than 2 mg/dl, or who required pharmacologic therapy for hypertension or diabetes were excluded from the study. Participants adhered to a diet that limited sodium to 200 mEq/day; those who maintained sodium balance (based on weight and 24-hr urine collection) were enrolled. Volunteers were randomized to receive rofecoxib 50 mg/day, indomethacin 50 mg 3 times/day, or placebo. After 2 weeks of therapy, their GFRs and creatinine clearances decreased significantly from baseline in the indomethacin group, but no differences were found in the rofecoxib and placebo groups. Urinary 6-keto-$PGF_{1\alpha}$, an index of the renal biosynthesis of prostacyclin, was significantly inhibited by indomethacin and rofecoxib but was not affected by placebo. Urinary sodium excretion was significantly decreased from baseline during the first 72 hours of treatment in the rofecoxib and indomethacin groups. This effect was not significantly different between the treatment groups. At day 14, there was no difference in urinary sodium excretion between participants receiving indomethacin, rofecoxib, or placebo. Selective COX-2 inhibition decreased renal prostacyclin synthesis to the same extent as nonselective COX-1 and COX-2 inhibition and transiently decreased sodium excretion independent of renal hemodynamics.

Similarly, the effects of naproxen and celecoxib on GFR and urinary PGE_2 and 6-keto-$PGF_{1\alpha}$ excretion were studied in 29 healthy elderly volunteers (mean ± SD age 70.1 ± 4.0 yrs).[20] In a crossover manner, participants received naproxen 500 mg twice/day for 10 days or celecoxib 200 mg twice/day for 5 days followed by 400 mg twice/day on days 6–10. Treatment sequences were separated by a 7-day washout period. Mean ± SD baseline GFR was 80.1 ± 12.8 ml/minute/1.73m^2 for patients receiving celecoxib first and 84.3 ± 14.2 ml/minute/1.73m^2 for patients receiving naproxen first. After the first treatment dose, naproxen decreased GFR by 6% (-5.3 ± 2.4 ml/min/1.73m^2), whereas GFR remained relatively unchanged with celecoxib 200 mg (-0.8 ± 1.7 ml/min/1.73m^2). The difference between the groups did not reach statistical significance until day 6, when GFR decreased by 9% with naproxen (-7.5 ± 2.4 ml/min/1.73m^2) and 1% (-1.1 ± 1.9 ml/min/1.73m^2) with celecoxib 400 mg (p=0.004). Both treatment groups had similar and sustained decreases in urinary PGE_2 and 6-keto-$PGF_{1\alpha}$. Based on the rationale that urinary PGE_2 and 6-keto-$PGF_{1\alpha}$ reflect mainly renal prostaglandin synthesis, the results of this study support previous in vitro[18] and clinical[19] evidence that COX-2 is constitutively expressed in the human kidney and has a role in the synthesis of renal prostaglandins. In both groups, urinary sodium excretion decreased significantly from baseline on day 1 of treatment (-38% for naproxen; -30% for celecoxib) and returned to comparable baseline levels by day 3. The similar effects on urinary sodium excretion between celecoxib and naproxen and the lack of GFR reduction by celecoxib suggest that COX-2 activity may be more specific for regulating renal sodium and water balance than hemodynamics in otherwise healthy elderly individuals. In healthy adults, GFR does not seem to depend on renal COX-2 activity.

The relative importance of COX-1 and COX-2 inhibition on renal hemodynamics and water balance in sodium-depleted individuals has been compared.[21, 22] In a double-blind, placebo-controlled study, 60 healthy elderly volunteers (age range 65–80 yrs) were randomized to receive a 5-day course of rofecoxib 12.5 mg/day, rofecoxib 25 mg/day, indomethacin 50 mg 3 times/day, or placebo.[21] Participants had creatinine clearances of 30–80 ml/minute and received a diet that limited sodium to 30 mEq/day. Glomerular filtration rate, measured on day 6, was significantly reduced in the groups receiving rofecoxib 12.5 mg and 25 mg compared with placebo (0.14 ml/sec, p=0.019, and 0.13 ml/sec, p=0.029, respectively) but did not reach statistical significance in the indomethacin group (0.10 ml/sec, p=0.086). Reductions in GFR among the treatment groups were not statistically significant (p>0.2). No changes in creatinine clearance between treatment groups or placebo were noted. Because a sodium-restricted diet in experimental conditions may mimic the intravascular volume status found in patients with chronic heart failure or cirrhosis or in patients receiving diuretic therapy, the results of this study may indicate that in predisposed individuals, selective COX-2 inhibition deteriorates renal function.

The renal effects of naproxen, celecoxib, and placebo were studied in 40 salt-depleted healthy men (age range 18–35 yrs).[22] Volunteers received a low-sodium diet (< 50 mEq/day) and were randomized in a double-blind manner to receive a 7-day course of celecoxib 200 mg twice/day, celecoxib 400 mg twice/day, naproxen 500 mg twice/day, or placebo. On day 1, a statistically significant decrease in GFR and renal plasma

flow was observed in the celecoxib 400 mg group compared with baseline, celecoxib 200 mg, and naproxen. Both effects, however, were transient, and no changes in GFR or renal plasma flow were observed on day 7. A significant decrease in urine output was seen after the first dose of celecoxib 200 mg and 400 mg compared with baseline and placebo; this decrease was comparable in the naproxen group. Urinary sodium excretion significantly decreased in the naproxen group and both celecoxib groups compared with placebo. This study suggests that the deleterious renal effects caused by selective COX-2 inhibition in sodium-depleted persons may not be limited to individuals with age-related decreases in GFR but may extend to healthy young adults as well.

Our conclusions from the findings of these four studies can be summarized as follows: COX-2 is constitutively expressed in the human kidney and is involved in the synthesis of renal prostaglandins; in otherwise healthy and non–sodium-depleted adults, COX-2 activity may more specifically regulate renal sodium and water balance than GFR; and COX-2 inhibition in predisposed individuals, such as those with age-related decreases in GFR or sodium depletion, may deteriorate renal function.

Several large randomized clinical trials have reported the frequency of renal adverse effects of selective COX-2 inhibitors.[1, 4, 5] A study comparing rofecoxib and naproxen in more than 8000 patients with rheumatoid arthritis reported that the frequency of renal adverse effects was similar between the groups (1.2% and 0.9% in the rofecoxib and naproxen groups, respectively) with only 0.2% of patients requiring discontinuation of therapy.[5] In a study comparing celecoxib with naproxen in more than 1000 patients, baseline serum creatinine concentrations (0.75 ± 0.19 mg/dl) were not affected by either agent and no adverse renal effects were reported.[1] The Celecoxib Long-Term Arthritis Safety Study (CLASS) reported a 5% frequency of renal effects (peripheral edema, hypertension, and increased serum creatinine) for the celecoxib group and 6.6% for the NSAIDs group ($p \leq 0.05$).[4] In this study, 0.9% of patients in the celecoxib group and 1.5% of patients in the NSAIDs group had increases in serum creatinine of 1.8 mg/dl or more, increases in serum urea nitrogen of 40 mg/dl or more, or both ($p=0.03$). Although the frequency of renal side effects with selective COX-2 inhibitors in these trials was low, it is important to note that patients with impaired renal or hepatic function or volume depletion were excluded from participating. More recently, a study using the World Health Organization/Uppsala Monitoring Centre Safety Database concluded that the adverse renal effects of celecoxib appear to be similar to those of traditional NSAIDs.[23] However, given the limitations of voluntary adverse drug reactions reporting, further epidemiologic or clinical studies are necessary to determine the accuracy of this conclusion.

Three cases of COX-2 inhibitor–associated acute renal failure have been reported in the literature.[24, 25] All three cases occurred in elderly patients who had comorbid conditions, such as chronic renal insufficiency, cardiomyopathy, or diabetic nephropathy. Our patient's significant history of cardiac disease and intense diuretic therapy and the relatively high dosage of rofecoxib prescribed predisposed her to acute renal failure. (Although our patient received the manufacturer's recommended dosage of 50 mg/day for managing acute pain, the recommended dosage for osteoarthritis is 12.5 mg/day, with a maximum of 25 mg/day.) In contrast to our patient, the patients in the previous reports had acute renal failure within 2 weeks of starting therapy. The rapid progression of our patient's renal failure with one dose of rofecoxib implicates the drug as the offending agent, especially when significant decreases in GFR with the first dose of COX-2 inhibitors have been reported in healthy elderly volunteers receiving sodium-depleted diets.[21]

Our patient arrived at the emergency department with stable blood pressure and no signs of pulmonary or peripheral edema. The presence of hyaline casts as well as a urine sodium concentration of 29 mEq/L during diuretic therapy suggested acute prerenal failure. The rapid return of her serum creatinine level to baseline after discontinuation of rofecoxib and hydration further implicate the agent as a precipitating factor of our patient's renal failure.

Although losartan has been associated with acute renal failure[26, 27] and may have contributed to our patient's prerenal clinical presentation, a temporal relationship cannot be established because no change in the patient's drug regimen was reported other than beginning rofecoxib and allopurinol 24 hours before presentation. In addition, our patient's clinical presentation was not consistent with allopurinol hypersensitivity syndrome. Although patients with this syndrome may develop some degree of renal dysfunction, they also develop toxic epidermal necrolysis,

erythema multiforme, or a diffuse maculopapular or exfoliative dermatitis, and at least one of the following symptoms: acute hepatocellular injury, marked eosinophilia, or worsening renal function.[28–32] Although our patient had decreased renal function, she did not have a rash, and a complete blood count with differential was normal.

The manufacturers of COX-2 inhibitors caution against the administration of these agents in patients with preexisting renal disease and considerable dehydration.[33–35] In addition, growing evidence suggests that COX-2 inhibitors should be prescribed with caution or not at all for patients in whom traditional NSAIDs pose a risk for renal failure, including those with heart failure, sodium depletion, and preexisting hepatic or renal insufficiency.

References

1. Simon LS, Weaver DY, Graham AJ, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis. JAMA 1999;282:1921–8.
2. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999;282:1929–33.
3. Emery P, Zeidler H, Kvien TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomized double blind comparison. Lancet 1999;354: 2106–11.
4. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. JAMA 2000;284:1247–55.
5. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520–8.
6. Day R, Morrison B, Leiza A, et al. A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. Arch Intern Med 2000;160:1781–7.
7. Cryer B, Kimmey M. Gastrointestinal side effects of nonsteroidal anti-inflammatory drugs. Am J Med 1998; 105(1B):20S–30.
8. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. N Engl J Med 1999;340:1888–99.
9. Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1984;310:563–72.
10. Schlondroff D. Renal complications of nonsteroidal anti-inflammatory drugs. Kidney Int 1993;44:643–53.
11. Perez Gutthann S, Garcia Rodriguez LA, Raiford DS, Duque Oliart A, Ris Romeu J. Nonsteroidal anti-inflammatory drugs and the risk of hospitalization for acute renal failure. Arch Intern Med 1996;156:2433–9.
12. Schneider A, Stahl RAK. Cyclooxygenase-2 (COX-2) and the kidney: current status and potential perspectives. Neprol Dial Transplant 1998;13:10–12.
13. Brater DC. Effects of nonsteroidal anti-inflammatory drugs on renal function: focus on cyclooxygenase-2-selective inhibition. Am J Med 1999;107(6A):65S–71.
14. Lipsky PE, Brooks P, Crofford LJ, et al. Unresolved issues in the role of cyclooxygenase-2 in normal physiologic processes and disease. Arch Intern Med 2000;160:913–20.
15. Harris RC, Mckanna JA, Akai Y, Jacobson HR, Dubois RN, Breyer MD. Cyclooxygenase-2 is associated with the macula densa of rat kidney and increases salt restriction. J Clin Invest 1994;94:2504–10.
16. Yang T, Singh I, Pham H, et al. Regulation of cyclooxygenase expression in the kidney by dietary salt intake. Am J Physiol 1997;274:F481–9.
17. Vio CP, Cespedes C, Gallardo P, Masferrer JL. Renal identification of cyclooxygenase-2 in a subset of thick ascending limb cells. Hypertension 1997;30(pt 2):687–92.
18. Komhoff M, Grone HJ, Klein T, Seyberth HW, Nusing RM. Localization of cyclooxygenase-1 and -2 in adult and fetal human kidney: implication for renal function. Am J Physiol 1997;272(4 pt 2):F460–8.
19. Catella-Lawson F, Mcadam B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther 1999;289:735–41.
20. Whelton A, Schulman G, Wallemark C, et al. Effects of celecoxib and naproxen on renal function in the elderly. Arch Intern Med 2000;160:1465–70.
21. Swan SK, Rudy DW, Lasseter KC, et al. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low salt diet. A randomized controlled trial. Ann Intern Med 2000;133:1–9.
22. Rossat J, Maillard M, Nussberger J, Brunner HR, Burnier M. Renal effects of selective cyclooxygenase-2 inhibition in normotensive salt-depleted subjects. Clin Pharmacol Ther 1999;66:76–84.
23. Zhao SZ, Renolds MW, Lefkowith J, Whelton A, Arellano FM. Comparison of renal-related adverse drug reactions between rofecoxib and celecoxib, based on the World Health Organization/Uppsala Monitoring Centre Safety Database. Clin Therap 2001;23:1478–91.
24. Perazella MA, Eras J. Are COX-2 inhibitors nephrotoxic? Am J Kidney Dis 2000;35:937–40.
25. Wolf G, Porth J, Stahl RA. Acute renal failure associated with rofecoxib [letter]. Ann Intern Med 2000;133:394.
26. Lamb RV, WaltonT. Acute renal failure after administration of losartan [letter]. West Virg Med J 1996;92:241.
27. OstermanM, Goldsmith DJ, Doyle T, Kingswood JC, Sharpstone P. Reversible acute renal failure induced by losartan in a renal transplant recipient. Post Grad Med J 1997;73:105–7.
28. Mills RM. Severe hypersensitivity reactions associated with allopurinol. JAMA 1971;216:799–802.
29. Young JL, Boswell RB, Nies AS. Severe allopurinol hypersensitivity association with thiazides and prior renal compromise. Arch Intern Med 1974;134:553–8.
30. Pluim HJ, VanDeuren M, Wetzels JF. The allopurinol hypersensitivity syndrome. Netherlands J Med 1998;52:107–10.
31. Kumar A, Edward N, White NI, Johnston PW, Catto GR. Lesson of the week: allopurinol, erythema multiforme, and renal insufficiency. BMJ 1996;312:173–4.
32. Arellano F, Sacristan JA. Allopurinol hypersensitivity syndrome: a review. Ann Pharmacother 1993;27:337–43.
33. Pfizer Inc. Celebrex (celecoxib) package insert. New York, NY; 2000.
34. Merck & Co., Inc. Vioxx (rofecoxib) package insert. West Point, PA; 2001.
35. Pharmacia Corporation. Bextra (valdecoxib) package insert. Chicago, IL; 2002.