Nephrotoxicity of Selective COX-2 Inhibitors

ALEXANDER WOYWODT, ANKE SCHWARZ, MICHAEL MENGEL, HERMANN HALLER, HENNING ZEIDLER, and LARS KÖHLER

ABSTRACT. We describe 2 male patients, a 49-year-old with psoriatic arthritis and impaired renal function and a 43-year-old renal transplant recipient, who both sustained a marked decline in glomerular filtration rate in conjunction with a selective inhibitor of cyclooxygenase-2 (COX-2), rofecoxib. In the second patient, acute renal failure necessitated hemodialysis. Both patients made an uneventful recovery. Our report lends further support to the assumption that COX-2 inhibitors, as a class, can be as nephrotoxic as their nonselective predecessors. Therefore, COX-2 inhibitors should be used with caution in renal transplant recipients and in patients with salt depletion and renal insufficiency. (J Rheumatol 2001;28:2133–5)

Key Indexing Terms:
CYCLOOXYGENASE INHIBITORS NEPHROTOXICITY

Nephrotoxic effects of non-selective cyclooxygenase inhibitors are abundantly documented1. Recently, selective inhibitors of cyclooxygenase-2 (COX-2) were introduced with considerable enthusiasm not only because of their improved gastroprotection, but also because they had initially been considered innocuous to renal function. This assumption was partly based on studies showing low COX-2 expression in healthy kidney tissue2. Indeed, nephrotoxicity was not observed in a trial of celecoxib in patients with normal renal function3. Other studies showed that both celecoxib and rofecoxib, when compared with nonselective COX inhibitors, did not impair renal function although both drugs caused sodium retention4,5. More recently, however, several findings have made physicians increasingly aware of potential renal side effects of these drugs. Presence of COX-2 has been documented in healthy renal tissue6. Moreover, a marked decline in glomerular filtration rate was reported in patients with salt depletion both with celecoxib7 and rofecoxib8. We report significant nephrotoxicity in conjunction with the selective COX-2 inhibitor rofecoxib in 2 patients.

CASE REPORT

Case 1. A 49-year-old male was admitted with chest pain and a history of coronary heart disease. Cardiac enzymes and thallium scans were normal, thus coronary angiography was withheld and chest pain improved spontaneously. The patient had renal insufficiency of unknown cause after right-sided nephrectomy had been performed in 1979. Medication included aspirin 100 mg, atorvastatin 20 mg, ranitidine 150 mg, atenolol 50 mg, hydrochlorothiazide 25 mg, isosorbide dinitrate 40 mg, paracetamol, which he took occasionally, and allopurinol 150 mg. None of the drugs had been introduced recently. Prior to admission, serum creatinine had been 145 μmol/l, potassium 4.4 mmol/l, creatinine clearance 76 ml/min, proteinuria 7 g per day and the left kidney had been 14 cm in size. Hypertensive nephrosclerosis, focal segmental glomerulosclerosis secondary to surgical loss of nephron mass, and IgA nephropathy were all included in the differential diagnosis. Renal biopsy had been contemplated previously but potential consequences of the result had not been regarded as substantial enough to warrant biopsy of a single kidney. The patient reported pain and swelling of knees and ankles. There was an inflammatory effusion of the left knee with 4100 leukocytes/ml and protein 3.56 g/dl. The patient had a history of lifelong psoriasis and a diagnosis of psoriatic arthritis was made. Rofecoxib (Vioxx™, Merck) 25 mg/day was substituted for paracetamol. During the following days, renal function deteriorated and serum creatinine peaked at 183 μmol/l (Figure 1). Urine microscopy and renal ultrasound were unremarkable. Serum potassium and sodium were normal and proteinuria was 1.14 g/l. Clinical examination showed no peripheral edema and blood pressure was normal. Common causes of a hospital-acquired decline in renal function were absent; in particular, there was no radiocontrast exposure and no other drugs other than rofecoxib had been begun. Hence, a tentative diagnosis of acute renal failure due to rofecoxib was made, the drug was stopped and renal function recovered.

Case 2. A 43-year-old male with polycystic kidney disease, who had received a cadaveric renal transplant in October 1999, was admitted in January 2000, with a rise in serum creatinine from 189 to 221 μmol/l. Medication included mycophenolate 3 g, prednisolone 20 mg, cyclosporine 200 mg, metropolol 100 mg, doxazosin 12 mg, furosemide 120 mg, ganciclovir 1.5 g, pantoprazole 40 mg and benapral 2.5 mg. None of the drugs had been introduced recently. Cyclosporine levels were within the therapeutic range. Clinical examination showed pitting edema. Urine microscopy and renal ultrasound were unrevealing. Serum electrolytes were normal with serum potassium between 4.5 and 4.8 mmol/l. Two consecutive renal biopsies showed mild interstitial edema and acute focal tubular damage. There was no evidence of rejection or interstitial nephritis. Serum creatinine rose to 548 μmol/l, uremic symptoms ensued and hemodialysis had to be instituted. Imaging studies showed moderate stenosis of the transplant renal artery. Scintigraphic studies, however,
showed no evidence of impaired perfusion. When a meticulous drug history was obtained, it was noted that the patient had received rofecoxib, 25 mg daily, for shoulder pain due to osteoarthritis of the glenohumeral joint during the week before admission. He had apparently taken the drug for 5 consecutive days until 4 days before admission; the rise in serum creatinine had first been noted on the day before admission. A diagnosis of acute renal failure due to rofecoxib was made and serum creatinine gradually returned to baseline values.

**DISCUSSION**

Considerable progress has been made in understanding the role of COX-2 in health and disease. Studies in knockout mice have demonstrated that COX-2 is pivotal to renal development⁸ and it has become increasingly clear from animal studies that COX-2 plays an important role in regulating salt and volume homeostasis¹⁰. In response to low luminal chloride concentrations, macula densa cells in the thick ascending part of the loop of Henle increase COX-2 expression by activation of a p38 MAP kinase pathway¹¹. Recent work has suggested that COX-2 is equally important to human renal function and significant nephrotoxicity of selective COX-2 inhibitors has been reported in salt-depleted patients⁷,⁸.

Moreover, 3 cases of renal impairment due to rofecoxib and celecoxib have already been reported in patients without salt depletion¹². In our 2 cases, significant nephrotoxicity was observed in association with the selective COX-2 inhibitor rofecoxib. We believe that, although a cause-and-effect relationship cannot be proven, both the temporal course of renal function and the fact that no other drugs had been introduced concurrently argue in favor of rofecoxib as the most likely cause of deteriorating renal function. Table 1 summarizes the 3 cases reported in the literature and 2 cases reported here. Both our patients had a remarkably short time of exposure to the drug. In the second patient, the serum creatinine continued to rise even after the medication was withdrawn. All 5 patients made a full renal recovery although temporary hemodialysis had to be instituted in 2 cases. We report the first patient who underwent renal biopsy and the second patient with acute renal failure necessitating hemodialysis.

Renal side effects of nonselective cyclooxygenase inhibitors include hyperkalemia, edema, interstitial nephritis, minimal change glomerular lesions and transient impairment of glomerular perfusion¹. Based upon available data, we hypothesize that the latter was present here. Hyperkalemia was absent in our patients while the second patient indeed had peripheral edema; renal biopsy in this patient revealed nonspecific changes with mild interstitial edema and acute focal tubular damage. No signs of acute rejection or interstitial nephritis were found.

Our report adds further evidence to the assumption that selective COX-2 inhibitors can be nephrotoxic¹³. While these drugs apparently confer little, if any, risk of nephrotoxicity in patients with normal renal function⁹, this may not be the case in salt-depleted individuals, patients with renal insufficiency, and renal transplant recipients. We speculate that the patients reported here had up-regulation of COX-2 thus rendering their kidneys vulnerable to selective COX-2 inhibition. For example, up-regulation of COX-2 might have occurred as a sequel to subtle volume and salt depletion since both patients reported here received diuretics. The
Table 1. Cases of nephrotoxicity reported in association with selective COX-2 inhibitors.

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Drug</th>
<th>Daily Dose (mg)</th>
<th>Duration (days)</th>
<th>Salt-depletion</th>
<th>Degree of Nephrotoxicity</th>
<th>Renal Biopsy</th>
<th>Outcome (renal function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>63/M</td>
<td>Celecoxib</td>
<td>400</td>
<td>16</td>
<td>No</td>
<td>Rise in serum creatinine; edema</td>
<td>No</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Perazella, et al[12] Case 1</td>
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</tr>
<tr>
<td>68/M</td>
<td>Celecoxib</td>
<td>400</td>
<td>13</td>
<td>No</td>
<td>Rise in serum creatinine; edema; Mild hyperkalemia</td>
<td>No</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Perazella, et al[12] Case 2</td>
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</tr>
<tr>
<td>73/F</td>
<td>Rofecoxib</td>
<td>25</td>
<td>14</td>
<td>No</td>
<td>Acute renal failure with 1 session of hemodialysis; marked hyperkalemia</td>
<td>No</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Perazella, et al[12] Case 3 (Added in proof)</td>
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<tr>
<td>49/M</td>
<td>Rofecoxib</td>
<td>25</td>
<td>2</td>
<td>No</td>
<td>Rise in serum creatinine</td>
<td>No (solitary kidney)</td>
<td>Full recovery</td>
</tr>
<tr>
<td>This report, Case 1</td>
<td></td>
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<tr>
<td>43/M</td>
<td>Rofecoxib</td>
<td>25</td>
<td>5</td>
<td>No</td>
<td>Acute renal failure with 3 sessions of hemodialysis; edema</td>
<td>Yes</td>
<td>Full recovery</td>
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<tr>
<td>This report, Case 2</td>
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Second patient could have sustained COX-2 up-regulation because prostaglandins counteract cyclosporine-induced renal vasoconstriction[14]. Angiotensin converting enzyme (ACE) inhibitors such as benalapril, which the second patient received for hypertension, have also been documented to increase renal COX-2 expression[15]. Congestive heart failure, cirrhosis and intrinsic renal disease such as the nephrotic syndrome are other well-established risk factors for nephrotoxicity due to nonselective COX inhibitors. Further studies will clarify whether these disorders also increase the risk of nephrotoxicity due to the coxibs.

We conclude that selective COX-2 inhibitors, as a class, should be used with caution in patients with salt depletion, renal insufficiency, and in renal transplant recipients.

REFERENCES