Acute renal failure and hyperkalaemia associated with cyclooxygenase-2 inhibitors

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Abstract

Background. The renal effects of cyclooxygenase-2 (COX-2) inhibitors have been incompletely elucidated, and acute renal failure (ARF) due to COX-2 inhibitors has been reported.

Methods. In order to determine the causes of ARF and hyperkalaemia in five patients during COX-2 inhibitor therapy, we carefully analysed case studies of consecutive in-patients or out-patients referred to our Renal Division over a 6-month period for ARF and hyperkalaemia who had recently received COX-2 inhibitors.

Results. ARF developed 2–3 weeks after COX-2 inhibitor therapy in five patients. The ARF was consistent with pre-renal azotaemia from renal hypoperfusion. Four patients were receiving the loop diuretic, furosemide. Four patients developed hyperkalaemia and decreased serum bicarbonate despite diuretic therapy, and one patient had changes in plasma renin activity and aldosterone levels consistent with reversible hyporeninaemic hypoaldosteronism. Renal failure was reversible after discontinuation of diuretics and COX-2 inhibitors.

Conclusions. COX-2 inhibitors may cause reversible ARF and hyperkalaemia in patients with oedematous conditions treated with low sodium diets and loop diuretics.

Keywords: acute renal failure; hyperkalaemia

Introduction

The cyclooxygenase-2 (COX-2) inhibitors, celecoxib and rofecoxib, are increasingly used to treat a variety of rheumatological conditions. Since the primary isoform of cyclooxygenase in gastrointestinal mucosa is COX-1 and not COX-2, these agents have the therapeutic advantage of decreasing inflammation at tissue sites, particularly in joints, while sparing the gastrointestinal mucosa due to continued prostaglandin production via the COX-1 isoform. However, COX-2 enzymes are also expressed at multiple nephron sites in the mammalian kidney, including the cortical thick ascending limb, macula densa, medullary interstitial cells, and the endothelium of arteries and veins and glomerular podocytes [1]. Thus, it is possible that inhibition of COX-2 enzymes may be associated with alterations in renal function.

Studies of the short-term renal effects of COX-2 inhibitors in healthy males or elderly patients on low sodium diets demonstrated transient decreases in renal blood flow and glomerular filtration rate (GFR) [2,3]. In contrast, studies in healthy, elderly patients on a normal salt diet treated with COX-2 inhibitors for 1 week showed no decrease in GFR, but significant reductions in sodium excretion [4,5]. Indeed, several hundred cases of acute renal failure (ARF) from celecoxib or rofecoxib have been reported to the FDA recently. The majority of these patients had additional risk factors for ARF including chronic kidney disease, acidosis, congestive heart failure (CHF), hypertension or diuretic use for oedema [6–8]. Acute tubulointerstitial nephritis has also been associated with both agents [9,10]. We now describe five patients who developed reversible ARF, hyperkalaemia and decreased serum bicarbonate during short-term administration of celecoxib and rofecoxib for arthritis who were evaluated carefully with tests of renal function in order to better identify the causes of ARF, hyperkalaemia and acidosis. Three patients had mild to moderate renal insufficiency before therapy with COX-2 inhibitors, all were on sodium-restricted diets, and four received loop diuretics.

Subjects and methods

The five patients in this study were identified by the authors as having ARF within weeks of receiving COX-2 inhibitor
drugs over a 6-month period from January 1 to July 1, 2000. During this period, there were 214 referrals for ARF, so these patients represented 2% of patients evaluated for ARF. Two were in-patients and three were out-patients. Serum electrolytes, blood urea nitrogen (BUN), creatinine and urinary electrolytes were measured by standard auto-analyser techniques. Urinary pH was measured by a Radiometer pH meter in three patients and by the dipstick method in two patients. Fractional sodium excretion was calculated by the standard formula: urinary sodium + serum sodium x serum creatinine + urinary creatinine x 100%. Fractional urea excretion was calculated by the standard formula: urinary urea nitrogen + BUN x the serum creatinine + urinary creatinine x 100%. The transtubular potassium gradient (TTKG) was calculated by the standard formula: urinary potassium + urine/plasma osmolality ratio + serum potassium. A value ≤ 4 during hyperkalaemia indicates diminished renal potassium excretion. The GFR was measured by iothalamate clearance in 2 patients, 24-h creatinine clearance in 2 patients, and estimated by the Cockcroft-Gault formula in one patient. Statistical analysis utilized the Student’s t-test for paired data. A P-value < 0.05 was considered significant.

Evaluations were performed in all five patients to exclude other causes of ARF. Serum C3 and C4 complement, antinuclear antibody, serum eosinophils, antineutrophil cytoplasmic antibody (ANCA) and serum and urinary immuno-fixation were measured utilizing standard laboratory techniques. Urinalyses and urinary eosinophils by Hansel fixation were measured utilizing standard laboratory antinuclear antibody, serum eosinophils, antineutrophil cyto-fixation were measured utilizing standard laboratory.

Patient 1
A 67-year-old woman was admitted to our hospital with nausea and fatigue. Her baseline serum creatinine was 1.5 mg/dl and baseline BUN was 35 mg/dl. Two weeks prior to admission, she was started on celecoxib 100 mg twice daily for chronic arthritis pain. She had a past history of type 2 diabetes for 5 years, CHF and hypertension. She was on a low sodium diet, furosemide 40 mg daily, but she was not receiving an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker. Physical examination showed no significant orthostatic blood pressure decrease, heart rate increase, decreased skin turgor or peripheral oedema, but mucous membranes were dry. There were no examination findings of CHF. BUN on admission was 90 mg/dl and serum creatinine was 2.8 mg/dl (Table 1), and furosemide and celecoxib were discontinued. Serum potassium was 6.1 mEq/l, serum bicarbonate 20 mEq/l, TTKG 3.0 and fractional urea excretion 31% (Table 1). Urinalysis showed +2 protein and no casts. On a 4 g sodium diet at that time, a supine plasma renin activity was 2.2 ng/ml/h and a supine plasma aldosterone was 6.6 ng/dl. All other tests for causes of ARF were normal except for an increased urine total protein/creatinine ratio of 0.8 possibly due to mild diabetic nephropathy. Two litres of normal saline 0.9% were administered for 1 day, and renal function, serum potassium and serum bicarbonate gradually returned to baseline over the next 2 weeks with a serum creatinine of 1.3 mg/dl 2 weeks later at an out-patient visit. Two months later, on a 4 g sodium diet, the serum potassium was 4.2 mEq/l, the supine plasma renin was 4.2 ng/ml/h and supine plasma aldosterone was 12.7 ng/ml. The GFR measured by 24-h creatinine clearance was 60 ml/min.

Patient 2
A 53-year-old woman with a past history of hypertension and bipolar disorder was placed on rofecoxib 25 mg daily for chronic arthritis pain. Four months earlier, she had developed ARF from acute tubular necrosis secondary to urosepsis. At the start of rofecoxib therapy, she was on a low sodium diet, metoprolol extended release, 50 mg daily, and her serum creatinine was 1.4 mg/dl, BUN 22 mg/dl and serum potassium 3.0 mEq/l. Three and a half weeks later, the BUN had risen to 47 mg/dl and serum creatinine had increased to 1.7 mg/dl. Physical examination showed no significant orthostatic blood pressure decrease, heart rate increase, decreased skin turgor or peripheral oedema. There were no dramatic findings suggestive of CHF. The fractional excretion of sodium was 0.5% with a urinary sodium of only 15 mEq/l. Fractional excretion of urea was also reduced to 35%. Serum potassium had risen to 5.6 mEq/l with a TTKG of 3.6 (Table 1). Urinalysis showed +1 protein and no casts, and all other tests for ARF were normal. Rofecoxib was discontinued and the patient’s renal function, serum potassium and serum bicarbonate had returned to baseline levels at an out-patient visit 2 weeks later. Two months later, a sodium iothalamate clearance was performed at the time the serum creatinine was 1.3 mg/dl, and the GFR was 36 ml/min.

Patient 3
A 61-year-old woman with a history of CHF treated with a low sodium diet, furosemide 80 mg daily and enalapril 10 mg daily was started on celecoxib 200 mg twice daily for fibromyalgia syndrome. At that time, her BUN was 20 mg/dl with a creatinine of 1.1 mg/dl. Three weeks later, the BUN rose to 142 mg/dl and serum creatinine increased to 3.5 mg/dl.

Table 1. Features of COX-2 inhibitor acute renal failure

<table>
<thead>
<tr>
<th>Patient</th>
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<th>3</th>
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<td>R</td>
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<tr>
<td>Na⁺ mEq/l</td>
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<td>144</td>
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<td>K⁺ mEq/l</td>
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<td>Cl⁻ mEq/l</td>
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<tr>
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<td>32</td>
<td>–</td>
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<tr>
<td>TTKG</td>
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C, celecoxib; R, rofecoxib; FE Na⁺, fractional excretion of sodium; FE Urea, fractional excretion of urea; TTKG, transtubular potassium gradient.
Physical examination showed no significant orthostatic blood pressure decrease, heart rate increase, decreased skin turgor or peripheral oedema. There were no findings suggestive of CHF. Serum potassium was 5.1 mEq/l, serum bicarbonate 17 mEq/l, the fractional excretion of sodium 1.2% and the fractional excretion of urea 34%. Urinalysis and all other tests for ARF were normal. Furosemide, enalapril and rofecoxib were discontinued and the patient’s renal function, serum potassium and serum bicarbonate had returned to normal at an out-patient visit 2 weeks later, with a BUN of 32 mg/dl and a serum creatinine of 1.3 mg/dl. Therapy with furosemide and enalapril was reinstated without changes in BUN, serum creatinine or potassium. Two months later, the GFR measured by creatinine clearance was 78 ml/min.

**Patient 4**

An 83-year-old male was admitted to the hospital for rotator cuff surgery. Two weeks prior to admission, he had been placed on rofecoxib 50 mg daily for shoulder pain, and he was continued on a low sodium diet and furosemide 80 mg daily for a history of CHF. No ACE inhibitors were utilized. On admission, the BUN was 88 mg/dl, serum creatinine 3.6 mg/dl, serum potassium 5.8 mEq/l, and serum HCO3 20 mEq/l. Physical examination showed no significant orthostatic blood pressure decrease, heart rate increase, decreased skin turgor or peripheral oedema. There were no findings suggestive of CHF. Urinalysis and all other tests for ARF were normal. Furosemide and rofecoxib were discontinued and 2 l of 0.9% normal saline were administered intravenously for 1 day. The serum creatinine gradually decreased to 1.8 mg/dl and potassium gradually decreased to 4.4 mEq/l over the next 2 weeks. The GFR estimated by the Cockcroft–Gault formula was 62 ml/min. The patient died before further renal testing could be performed.

**Patient 5**

A 52-year-old male was placed on rofecoxib 25 mg for arthritis pain. He had been treated for hypertension and venous insufficiency for many years with a low sodium diet, furosemide 40 mg bid and hydrochlorothiazide 25 mg daily. Three weeks after rofecoxib, the BUN increased to 66 mg/dl from a baseline of 22 mg/dl, and the serum creatinine increased to 2.4 mg/dl from a baseline of 1.1 mg/dl. Physical examination showed no significant orthostatic blood pressure decrease, heart rate increase, decreased skin turgor or peripheral oedema. There were no dramatic findings suggestive of CHF. The serum potassium was below normal, 3.4 mEq/l, despite acute failure, and serum bicarbonate was normal, 27 mEq/l. Furosemide, hydrochlorothiazide and rofecoxib were discontinued. The patient’s renal function had returned to normal at an out-patient visit 2 weeks after discontinuing these drugs. Both diuretics have been restarted without significant changes in BUN, serum creatinine or serum potassium. The sodium iothalamate clearance performed 4 weeks later was 95 ml/min.

**Results**

The results of serum C3 and C4 complement, antinuclear antibody, serum and urinary eosinophils, ANCA, serum and urinary immunofixation studies, urinalyses and renal ultrasound examinations were normal in all five patients. The effects of COX-2 inhibitors on serum creatinine and serum potassium are illustrated in Figure 1. The mean serum creatinine before COX-2 inhibition was 1.3±0.2 mg/dl which increased to 2.8±0.4 mg/dl during COX-2 inhibition and recovered to a mean of 1.4±0.2 mg/dl 2–3 weeks later (P = 0.02 compared with baseline; P = 0.04 compared with recovery). Patients 1, 2 and 4 had chronic renal failure with GFRs of 60, 36 and 62 ml/min, respectively. The mean serum potassium at the time of ARF was 5.2±0.6 mEq/l and decreased to 4.2±0.4 mEq/l after COX-2 inhibitors were discontinued. (P = 0.03). One patient was hypokalaemic despite acute azotaemia while receiving two diuretics for hypertension. During ARF, serum bicarbonate decreased significantly to a mean of 21±2 mEq/l, and increased to 27±1 mEq/l 2–3 weeks later; P < 0.05. Four patients developed a significant decrease in serum bicarbonate associated with urinary pH < 5.5, suggesting the possibility of type IV renal tubular acidosis. The mean anion gap before the drug was 11±2 and 12±3 during ARF, and 11±3 in recovery; P > 0.05.

![Fig. 1. Effects of COX-2 inhibitor on serum creatinine and serum potassium. *P = 0.02 ARF compared with baseline; P = 0.04 ARF compared with recovery. †P = 0.03 ARF compared with recovery.](https://academic.oup.com/ndt/article-abstract/19/5/1149/1805653/fig1)
Discussion

All five patients developed ARF which was reversible upon discontinuing diuretics and COX-2 inhibitors. Two patients may have been slightly depleted of sodium or water and received intravenous saline, but none of the patients had haemodynamic signs of volume depletion, and the ARF resolved in those two patients slowly over 2 weeks. The most likely cause of ARF in these patients was pre-renal azotaemia secondary to renal hypoperfusion. Other causes of ARF, including acute tubular necrosis, vasculitis, glomerulonephritis and urinary tract obstruction, were excluded by the diagnostic work-up. The low fractional excretion of urea in four patients was consistent with a diagnosis of renal hypoperfusion. Urinary sodium and fractional excretion of sodium were not helpful because the majority of patients were already on loop diuretics, which could raise the fractional excretion of sodium to >1% despite pre-renal azotaemia. However, acute interstitial nephritis could not be definitely excluded since renal biopsies were not performed.

Recent data suggest that COX-2 enzyme expression in mammalian kidney is increased by decreases in extracellular fluid volume induced by sodium restriction and diuretics [1]. Loop diuretics impair sodium chloride reabsorption in the loop of Henle and enhance excretion of sodium and chloride by as much as 30%, which can lead to reduced renal blood flow and GFR from contraction of the extracellular fluid volume. In addition, furosemide has been shown to stimulate macula densa COX-2 expression in mammalian kidney, and enhanced COX-2 expression has been demonstrated in the macula densa of patients with Bartter’s syndrome, a disorder of impaired NaCl reabsorption in the thick ascending loop of Henle [11,12]. Moreover, COX-2-stimulated prostaglandins attenuate glomerular arteriolar constriction associated with tubular glomerular feedback in a paracrine fashion [13,14]. This protective mechanism maintaining glomerular perfusion may be attenuated by COX-2 inhibitors, leading to sustained glomerular arteriolar constriction, renal hypoperfusion and pre-renal azotaemia. The low fractional excretion of urea in the majority of patients in this study supports the diagnosis of renal hypoperfusion. However, confirmation of these mechanisms must await further studies.

Four patients developed hyperkalaemia associated with a significant decrease in serum bicarbonate, which suggests the presence of non-anion gap metabolic acidosis, but venous or arterial pHs were not measured. It is possible that hyperkalaemia in these patients could have contributed to the metabolic acidosis by impairing urinary ammonia production which would limit net acid excretion [15]. In addition, the first patient developed low normal supine plasma renin and aldosterone levels while on celecoxib which significantly increased off this drug. This patient probably had diabetic nephropathy with a GFR of 60 ml/min and mild proteinuria, making her more likely to develop hyporeninaemic hypoaldosteronism. However, plasma renin activity and plasma aldosterone stimulation tests with furosemide and upright posture or after cosyntropin were not performed. This case is similar to reports of non-selective COX inhibitors inducing the syndrome of hyporeninaemic hypoaldosteronism, hyperkalaemia and metabolic acidosis [16]. Indeed, COX-2 isoforms also mediate renin release in the mammalian nephron. COX-2 enzymes regulate the increased juxtaglomerular renin content induced by a low sodium diet in an animal model, and inhibition of COX-2 isoforms inhibits macula densa-stimulated renin release associated with a low sodium diet [17,18]. In addition, in healthy individuals, furosemide stimulates renin release from the macula densa which is significantly diminished by COX-2 inhibitors [19].

Thus, a proximate cause for hyporeninaemic hypoaldosteronism in patients on COX-2 inhibitors could be inhibition of renin release. However, prostaglandins may also mediate angiotensin II-stimulated aldosterone release, but whether COX-2 inhibition alters these mechanisms is unknown. Three patients had a TTKG <4, which is consistent with diminished aldosterone effects on urinary potassium secretion in the distal nephron despite the concomitant use of loop diuretics in two of these patients.

In summary, we have shown that reversible ARF can occur in oedematous patients treated with a low sodium diet, loop diuretics and COX-2 inhibitors. Renal failure from COX-2 inhibitors is associated with hyperkalaemia which may be caused by the syndrome of hyporeninaemic hypoaldosteronism. Although the majority of healthy patients treated with COX-2 inhibitors have no deterioration in renal function or electrolyte balance [20], patients with oedematous conditions requiring dietary sodium restriction and/or diuretics, especially loop diuretics, such as chronic renal insufficiency, CHF, chronic liver disease and hypertension, should be treated cautiously with COX-2 inhibitors. Electrolytes and renal function should be checked 1–2 weeks after initiation of COX-2 inhibitors in these patients to screen for hyperkalaemia and ARF. The potential risks of COX-2 inhibitors in these patients should be weighed before prescribing these drugs as long-term therapy.

Conflict of interest statement. None declared.

References


Received for publication: 15.1.03
Accepted in revised form: 22.10.03