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Renal Failure Associated with the Use of Celecoxib and Rofecoxib

Syed R. Ahmad, Cindy Kortepeter, Allen Brinker, Min Chen and *Julie Beitz*

Division of Drug Risk Evaluation, Office of Drug Safety, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland, USA

Abstract

Objective: Celecoxib and rofecoxib are two relatively new nonsteroidal anti-inflammatory drugs (NSAIDs) that selectively inhibit the cyclo-oxygenase-2 (COX-2) isoenzyme at therapeutic concentrations. The nephrotoxic potential of selective COX-2 inhibitors has not been clearly established. This study was conducted in order to understand the association between acute renal failure and the two COX-2 inhibitors celecoxib and rofecoxib.

Methods: A search was performed in the US Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS) to identify cases of renal failure submitted to the FDA. A MEDLINE search of the English language literature was also performed to identify published cases of renal failure associated with celecoxib and rofecoxib.

Results: One hundred twenty-two and 142 domestic US cases of celecoxib and rofecoxib-associated renal failure, respectively, were identified in the AERS database. The literature search identified 19 cases of acute renal impairment in association with celecoxib and rofecoxib. In addition, drug regulatory authorities in the UK, Canada, and Australia have received about 50 reports of renal failure with celecoxib and rofecoxib. Descriptive statistics of the AERS cases have been summarised in this report.

Conclusions: Data from AERS and published case reports suggest that use of both these drugs is associated with renal effects similar to that of conventional nonselective NSAIDs. Physicians should be aware that serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short-term therapy with celecoxib and rofecoxib. Patients at greatest risk for renal injury are those with pre-existing renal impairment, heart failure, liver dysfunction, those taking diuretics and/or ACE inhibitors, and the elderly. Kidney function should be monitored closely for any signs of potential renal injuries soon after initiating treatment with these agents, especially in high-risk populations. In addition, healthcare practitioners should adequately warn patients of the signs and symptoms of serious renal toxicity, and of the need for them to see their physician promptly if they occur. Celecoxib and rofecoxib are not recommended for use in patients with advanced renal disease.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for the management of pain and inflammation. The use of conventional NSAIDs has been associated with serious gastrointestinal adverse events including ulceration, bleeding, and perforation. Celecoxib and rofecoxib are the first two members of selective cyclo-oxygenase-2 (COX-2) inhibitors that were approved for marketing by the US Food and Drug Administration (FDA) in December 1998 and May 1999, respectively. The selective COX-2 inhibitors or coxibs were developed largely with the belief that these drugs will have a better safety profile than the conventional NSAIDs.[1,2] Two large randomised controlled clinical trials have been published that examined the efficacy and safety of celecoxib and rofecoxib.[3,4] Neither study [Celecoxib Long-Term Arthritis Safety Study (CLASS) nor Vioxx Gastrointestinal Outcomes Research (VIGOR)] reported celecoxib or rofecoxib to have a clinically significant advantage over conventional NSAIDs in terms of general safety or tolerability as reflected in endpoints such as withdrawals due to adverse events.[5]

After the gastrointestinal tract, the kidneys are the second most frequent organ affected by adverse events associated with NSAID use.[6] The renal adverse effects of NSAIDs include decreased renal perfusion, decreased glomerular filtration rate, decreased sodium/potassium excretion, oedema, increased blood pressure, and interstitial nephritis.[7-9] The nephrotoxic potential of selective COX-2 inhibitors has not been clearly established. COX-2 is expressed in the human kidney and has a role in normal renal physiology. Experimental evidence suggests that the profile of renal actions of selective COX-2 inhibitors is similar to that of conventional NSAIDs.[10]

In order to understand the association between acute renal failure and the two COX-2 inhibitors celecoxib and rofecoxib, we summarise cases reported to the FDA's spontaneous reporting system database known as Adverse Event Reporting System (AERS).

Materials and Methods

The FDA receives spontaneous reports of adverse drug events primarily from physicians, pharmacists and consumers, either directly or via pharmaceutical manufacturers. Reports are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology[11] and entered in into AERS. In recent years, the FDA received approximately 250 000 adverse event reports annually. From 1969, when FDA's spontaneous reporting system was first launched, to the present, the AERS database has accumulated over 2 million reports. A computerised search of the AERS database identified cases of renal failure in association with celecoxib and rofecoxib.

Method of Selection of Adverse Event Reporting System (AERS) Cases

We searched the AERS database using the following MedDRA terms: renal failure and impairment; renal vascular and ischaemic conditions; and nephropathies. The search included all reports entered into AERS up to October 2000.

Case Definition of Renal Failure

To accommodate the various ways in which renal failure was annotated in the adverse event reports, we defined renal failure as:

- a rise in serum creatinine of ≥0.5 mg/dl, if the baseline serum creatinine is <3.0 mg/dl; or
- a rise in serum creatinine of ≥1.0 mg/dl, if the baseline serum creatinine is ≥3.0 mg/dl; or
- a ≥20% decline in recovery serum creatinine from peak serum creatinine; or
- a peak serum creatinine of ≥2 mg/dl and one or more events from the sign/symptom list is mentioned (see below for sign/symptom list); or
- a rise in blood urea nitrogen (BUN) (>25 mg/dl) and one or more events from the sign/symptom list is mentioned (see 'sign/symptom' list section); or
- any case requiring phosphate binders (i.e. calcium, aluminium) or potassium-binding resins or sodium bicarbonate (to correct acidosis); or

- any case requiring dialysis or kidney transplant; or
- any case with a reported diagnosis of renal failure or acute renal failure.

Sign/Symptom List

Events in the sign and sympton list were as follows: decreased urinary output; increased blood pressure; increased potassium (serum potassium >5.1 mmol/L); decreased sodium (serum sodium <135 mmol/L); hyperphosphataemia; metabolic acidosis (serum bicarbonate <20 mmol/L); azotaemia; uraemia; oedema; symptoms of congestive heart failure.

Renal failure cases included reports of renal failure, acute renal failure, or any renal insufficiency with adequate data consistent with the case definition. Additionally, all cases had to have a temporal relationship with the intake of celecoxib or rofecoxib and an outcome consistent with our case definition of renal failure.

We used the following criteria to exclude cases:

- events not related to the drug administration, e.g. renal failure reported while patient had car accident and went into multi-organ failure
- events resulting from a previously existing underlying renal disorder
- events more related to (or confounded by) another suspect drug (two suspects reported) or concomitant drug(s), based on their therapy dates, and the other drug(s) is labelled for renal failure
- events for which causality cannot be assessed due to multiple suspect drugs (three or more)
- no evidence that the patient received the drug, including unconfirmed second hand report
- no evidence that the event of interest occurred including unconfirmed second hand report (i.e. reporter was notified by competitor's drug representative)
- evidence of hepatorenal syndrome (concomitant liver and renal failure)
- renal failure precipitated by concomitant rhabdomyolysis, or acute gastrointestinal bleeding, or sepsis
- fluid retention with no indication of renal failure
- event did not meet our case definition for renal failure.

We also reviewed published cases of renal failure reported in association with celecoxib and rofecoxib. A MEDLINE search of the English language literature was performed (June, 2002) using the following terms to identify published cases of renal failure with celecoxib and rofecoxib: kidney; renal failure; and renal toxicity.

Results

Review of Cases in AERS

A total of 630 reports (256 reports with celecoxib and 374 with rofecoxib) of renal events were identified from the search of AERS. A hands-on review of these reports identified 122 and 142 unduplicated domestic reports of renal failure associated with celecoxib and rofecoxib, respectively. Descriptive statistics for the renal failure case series are provided in table I. A summary of the cases for each drug case series will be outlined.

Celecoxib Case Series

In the celecoxib case series, the median age was 72 years (see table I). Age and gender were not stated in 18 and 14 reports, respectively. Among the cases where gender was reported, there was a preponderance of females. Of the 81 (66%) cases that mentioned time to onset of adverse renal symptoms from the start of celecoxib therapy, the median time was 18 days. In four (5%) cases, the time of onset was less than or equal to 3 days and in 33 (41%) cases, this was less than or equal to 14 days. Dosage was mentioned in 88 (72%) reports and it was within the labelling recommendation in all patients except one. One patient received 400mg twice daily, at least twice the recommended dose of celecoxib for his unspecified backache (an off-label indication in the US) and osteoarthrosis.

Serum creatinine (SCr) changes (peak SCr minus baseline SCr) were reported in 44 cases (36%). The mean SCr change was 2.9 mg/dl (range

Table I. Descriptive statistics for the renal failure case series (based on cases with the selected data element; i.e. null values excluded)[a]

		Celecoxib (n = 122)	Rofecoxib (n = 142)
Age (y)	Median	72	75
	Mean	69.7	73.1
	Range	14-101	33-101
Sex	% female	62.0	68.5
	% male	38.0	31.5
Onset (days)	Median	18	10
	Mean	41.7	32.7
	Range	1-300	1-450
No. of cases with onset at	≤3 days	4	32
	≤14 days	33	65
Creatinine change (baseline to peak; mg/dl)	Median	2.4	3.3
	Mean	2.9	4.0
	Range	0.5-7.6	0.4-12.9
Outcome[b] (% appearance)		Hospitalisation (64.0)	Hospitalisation (69.9)
		Life threatening (19.7)	Life threatening (23.1)
		Dialysis (12.3)	Dialysis (15.4)
		Death (6.6)	Death (6.3)
Dose (mg/day)	Median	200	25
	Mean	224	26.6
	Range	100-800	12.5-50
No. of cases	Greater than the recommended dose[c]	1	0

a Based on cases received through 10/26/2000.

b A case may report more than one outcome.

c >400 mg/day for celecoxib; >50 mg/day for rofecoxib.

0.5 to 7.6 mg/dl). In all 30 cases where SCr changes were reported as 2 mg/dl or above, the reported total daily dose of celecoxib was within the recommended dosage. Those cases reporting a peak and recovery serum creatinine (37 cases, 30%) noted an average decline of 1.8 mg/dl (range = 0.5 to 4.5 mg/dl) to recovery. Positive dechallenge was noted in 55 (45%) cases. Positive rechallenge was reported in two cases and these are described later. Sixty-four percent of the patients were hospitalised and 12% underwent dialysis. In nearly 20% of cases, the reporter considered the adverse renal event to be life-threatening. Eight (6%) patients who experienced renal failure died and the reporters suspected celecoxib to have played a role in their death. Forty-five cases reported a baseline SCr. Of the 45 cases, 15 (33%) had a baseline SCr ≤1.0 mg/dl, 27 (60%) had a baseline SCr ≤1.2 mg/dl, and 32 (71%) had a baseline SCr ≤1.5 mg/dl.

There were two cases with apparently normal kidney function and no history of renal disease who experienced renal failure. Subsequent to the initiation of celecoxib, the time to onset of renal failure was 4 days in one case and 30 days in the other. All cases presented with risk factors for renal failure aside from celecoxib use with the exception of 26 (21%) case reports, which did not state any risk factors. Of the 96 cases reporting risk factors, the most prevalent medical condition reported was hypertension (39%), followed by diabetes mellitus (29%), congestive heart failure (22%) and pre-existing or history of renal failure or renal in-

sufficiency (21%). Among patients with pre-existing renal disease, worsening of the patient's renal status was observed. Co-prescription of diuretics (39%) was most common, followed by ACE inhibitors (19%), and/or recent use of other NSAIDs (5%).

Two representative cases are as follows. A 78-year-old female with a history of hypertension, coronary artery disease, diabetes mellitus, and peripheral neuropathy was started treatment with celecoxib 200mg (at an unspecified frequency) for osteoarthritis. Her baseline SCr was 1.1 mg/dl and BUN was 16 mg/dl. Approximately 120 days later, her SCr increased to 3.1 mg/dl and BUN to 40 mg/dl and her medications, namely celecoxib, captopril, and hydrochlorothiazide were discontinued. At that time she was also taking cotrimoxazole (trimethoprim-sulfamethoxazole) for a urinary tract infection and this drug was also discontinued. About 35 days later her SCr was 1.2 mg/dl and BUN 20 mg/dl. Nearly 2 months later, her SCr was 1.2 mg/dl and BUN 29 mg/dl and celecoxib 100mg daily was restarted. About 12 days later her SCr increased to 2.0 mg/dl and BUN to 42 mg/dl and celecoxib was discontinued. A week later her SCr was 1.4 mg/dl and BUN was 30 mg/dl. Other concomitant medications that were not discontinued included atenolol, simvastatin, insulin and sertraline.

A physician reported that an 88-year-old female who was receiving celecoxib for an unspecified disease, dose and duration experienced acute renal failure for which she was hospitalised for 10 days. According to her physician, the acute renal failure resolved rapidly after unspecified therapy. Within a month, the physician restarted her on celecoxib and she was hospitalised again with acute renal failure and had to undergo dialysis. Her SCr rose to 4.3 mg/dl and BUN to 58 mg/dl. Celecoxib was discontinued and she again responded to unspecified therapy. There is no mention of concomitant illness or medications.

Rofecoxib Case Series

In the rofecoxib case series, the median age was 75 years (see table I). Twenty-nine cases (20%) did not report age and 18 cases (13%) did not report gender. Among the cases where gender was reported, there was a preponderance of females. The dosage of rofecoxib was reported in 103 cases and fell within the recommended range of 12.5 to 50 mg/day with a mean of 26.6 mg/day and a median of 25mg/day. The onset of adverse renal symptoms was reported in 100 cases and occurred at an average of approximately 33 days after the initiation of rofecoxib; however, the median was 10 days. Thirty-two (32%) cases occurred within 3 days and 65 (65%) cases occurred within 14 days. Fifty-two cases noted a baseline and peak SCr which showed a mean SCr change of 4.0 mg/dl (range = 0.4 to 12.9 mg/dl). Those cases reporting a peak and recovery SCr (45 cases, 32%) noted an average decline of 2.8 mg/dl (range = 0.4 to 11.1 mg/dl) to recovery. There were only 2 rechallenge cases where one was positive and the other negative at the time of reporting. Nearly 70% of the cases required hospitalisation and 15% reported the need for dialysis. Death occurred in nine (6%) cases and the reporters suspected rofecoxib-associated renal failure as a contributory factor.

Of the 142 cases, 12 reported normal kidney function or no history of renal dysfunction prior to initiating rofecoxib. Fifty-four cases reported a baseline SCr. Of the 54 cases, 10 (19%) had a baseline SCr ≤1.0 mg/dl, 16 (30%) had a baseline SCr ≤1.2 mg/dl, and 30 (56%) had a baseline SCr ≤1.5 mg/dl.

Common risk factors consist of concomitant disease states and medications and were multiple for most patients. Of the 112 cases reporting risk factors, the most prevalent medical condition reported was hypertension (33%), followed by diabetes mellitus (27%), pre-existing or history of renal failure or renal insufficiency (25%), and congestive heart failure (21%). Co-prescription of diuretics was most common (54%), followed by con-

comitant or recent use of selective or nonselective NSAIDs (42%), and ACE inhibitors (36%).

Two representative cases are as follows. A 79-year-old female with concurrent diabetes mellitus, lymph and peripheral oedema, atherosclerotic heart disease, and a prior mastectomy was placed on rofecoxib for osteoarthritis. Concomitant medications included furosemide (frusemide), metolazone, potassium, and lisinopril. The patient was admitted to the hospital 3.5 weeks later for oedema. Laboratory tests showed a SCr of 4.3 mg/dl, BUN of 97 mg/dl, potassium of 6.8 mmol/L, and phosphorus of 7.2 mg/dl. The nephrologist diagnosed acute renal failure and hyperkalaemia due to furosemide, lisinopril, rofecoxib, and potassium. Rofecoxib was discontinued and the patient was stabilised and discharged one week later. The patient restarted rofecoxib without the physician's consent and, again, experienced acute renal failure (SCr = 8.3 mg/dl, BUN = 65 mg/dl, potassium = 5.5 mmol/L, phosphorus = 10.6 mg/dl).

A 73-year-old female with multiple medical problems including osteoporosis, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, asthma, and angina developed renal failure, congestive heart failure, digoxin toxicity, and thrombocytopenia after 1 week of rofecoxib. Admission laboratory values revealed a SCr of 2.2 mg/dl, BUN of 50 mg/dl, pH of 7.1, potassium of 7.0 mmol/L, and a digoxin concentration of 5.6 ng/ml (baseline laboratory values: SCr = 1.7 mg/dl, BUN = 25 to 28 mg/dl, and digoxin <2.0 ng/ml). She experienced a cardiac arrest and was intubated and revived. She also required haemodialysis.

Review of the Literature

A MEDLINE search of the English language literature identified 20 cases (11 celecoxib, 9 rofecoxib) of acute renal impairment in association with celecoxib and rofecoxib.[12-21]

In addition, drug regulatory authorities in the UK, Canada, and Australia have received about 50 reports of renal failure associated with celecoxib and rofecoxib .[22-25]

Discussion

Adverse renal effects with the use of conventional NSAIDs is widely recognised and appreciated.[26-28] However, the risk of serious renal toxicity is relatively low. Nonetheless, up to approximately 5% of individuals exposed to NSAIDs may develop some adverse renal outcome.[29] While the risk is uncommon in healthy individuals, the incidence can approach 20% in patients at high risk.[30] In the US, an estimated 0.5 to 2.5 million individuals each year have the potential to manifest an NSAID-related renal adverse effect syndrome.[31]

Spontaneous reporting systems are an excellent means to detect the occurrence of rare adverse events in spite of limitations including extensive underreporting and inadequate or missing information in the reports. Our evaluation of the postmarketing adverse event reports of renal toxicity with the selective COX-2 inhibitors revealed serious or life-threatening renal toxicity including acute renal failure in association with the use of both celecoxib and rofecoxib. Although the greatest risk of acute renal failure with these drugs was observed in patients with multiple risk factors, there were also cases reported in patients with apparently normal kidney function. A small fraction of the cases had an acute onset of renal failure occurring within 3 days. Our findings are consistent with the literature reports of adverse renal events associated with these drugs. Selective COX-2 inhibitors, celecoxib and rofecoxib may not offer distinct advantages over conventional NSAIDs with respect to renal regulation of sodium excretion, blood pressure, and glomerular filtration rate and should be used with caution or avoided in patients with predisposing diseases.[32,33]

Conclusions

In summary, cases of acute renal failure in association with the use of both celecoxib and rofecoxib

have been reported to the FDA. Additionally, there have been published reports of renal impairment in association with these drugs. These data suggest that the newer drugs, celecoxib and rofecoxib, share the propensity of conventional nonselective NSAIDs to cause adverse renal events. These findings are also in accord with experimental evidence which suggests that the profile of renal actions of COX-2 inhibitors is similar to conventional NSAIDs.[10]

Physicians should be aware that serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short-term therapy. As stated in the current US labelling for celecoxib and rofecoxib, patients at greatest risk for renal injury are those with pre-existing renal impairment, heart failure, liver dysfunction, those taking diuretics and/or ACE inhibitors, and the elderly. Kidney function should be monitored closely for any signs of potential renal injuries soon after initiating treatment with selective COX-2 inhibitors, especially in high-risk populations. In addition, healthcare practitioners should adequately warn patients of the signs and symptoms of serious renal toxicity, and of the need for them to see their physician promptly if they occur. Celecoxib and rofecoxib are not recommended in patients with advanced renal disease.

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Correspondence and offprints: Dr *Syed R. Ahmad*, Division of Drug Risk Evaluation, Office of Drug Safety, Center for Drug Evaluation and Research, Food and Drug Administration, HDF-430, Room 15B-08, 5600 Fishers Lane, Rockville, MD 20857, USA.
E-mail: ahmads@cder.fda.gov