# Acute Congestive Heart Failure Induced by Rofecoxib

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are routinely prescribed for the treatment of various conditions requiring analgesia and anti-inflammatory activity. People also have access to NSAIDs over-the-counter for relief of mild aches, pains, and headaches. NSAIDs have the potential to produce several adverse effects in patients. They are known to have the potential to produce gastrointestinal toxicities leading to dyspepsia or even ulceration. Gastrointestinal symptoms are the most common adverse effects associated with NSAID use.[1] Platelet aggregation is known to be inhibited by NSAIDs because of their ability to inhibit the action of thromboxane A, a potent platelet aggregator.[2–4] This could lead to hemorrhaging in patients with vascular injuries or congenital hematologic conditions. Some patients may display allergic reactions to NSAIDs, possibly as severe as anaphylaxis. Further, NSAID-induced nephropathy may also occur in patients.[5–7] These complications may include renal injuries such as acute tubular necrosis and chronic interstitial nephritis. They may produce hemodynamic effects by promoting the retention of salt and water within patients.[8–10] This may result from their activity on renal prostaglandins, leading to edema and reduction in the effectiveness of antihypertensive regimens.[8,10,11] Despite these possible adverse effects, NSAIDs remain a first-line therapeutic alternative for patients suffering painful ailments.

NSAIDs act by inhibiting synthesis of prostaglandins from arachidonic acid via cyclooxygenase COX-1 and COX-2, the 2 isoforms of cyclooxygenase. COX-1 is constitutively found in normal cells and tissues throughout the body, with a dominant expression in the stomach. The expression of COX-1 in the stomach is believed to have protective properties of the gastric mucosa.[12,13] COX-2 is expressed in response to inflammatory stimuli, and is affected by cytokines and other inflammatory mediators. Most NSAIDs inhibit both isoforms to varying degrees, relative to the activity of the individual chemical properties of the NSAID. In recent years, COX-2 specific inhibitors have become available [celecoxib, rofecoxib, valdecoxib (in order of US market release)]. It had been hypothesized that by targeting the COX-2 enzyme specifically, only the inflammatory prostaglandins would be inhibited while sparing the activity of COX-1. This would allow the medication to produce anti-inflammatory and analgesia activities without potentially decreasing the protective effects of the COX-1 enzyme. It was also hypothesized that it may offer an improved renal safety profile in patients at risk for NSAID-induced renal toxicity.[14] Some studies have now suggested that renal injury may result secondary to COX-2 inhibitors.[15] Thus, the clinical development of COX-2 inhibitors theoretically improved the overall safety profile for patients while producing the clinical benefits of inflammation management in affected patients.

We report the case of a patient that presented with acute congestive heart failure (CHF) symptoms associated with COX-2 inhibitor use. We also offer possible explanations for the CHF onset secondary to COX-2 inhibitor use and management techniques and pharmacologic considerations for this situation from a primary care standpoint.

## Case Reports

A 42-year-old woman sought treatment from an orthopedist that she had been referred to for bilateral knee arthritis. Her medical history included severe sleep apnea, reasonably controlled hypertension, asthma, allergic rhinitis, gastroesophageal reflux disease, urinary incontinence, thalassemia minor, and depression. Long-term medications included loratadine, omeprazole, oxybutynin, sertraline, an estradiol/norethindrone oral contraceptive,

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atenolol, albuterol, and alprazolam. She used nasal continuous positive airway pressure device at night. For treatment of her knee osteoarthritis, she had been on 25 mg/day rofecoxib for several weeks when she had last seen her orthopedist 1 week before. At that visit, the orthopedist increased her rofecoxib to 50 mg/day.

Seven days later, she presented to the clinic with the chief complaint of "I'm short of breath." She described a 1-day history of coughing up foamy blood-tinged sputum, swelling of her lower extremities, dyspnea on exertion, 3-pillow orthopnea, and a "rattling in the chest" with coughing. She denied any fever, sore throat, myalgias, chest pain, or syncope. Her height was 5′ 5″; weight, 290 lbs; BMI, 48; temperature, 98.0°F; pulse, 69 beats/min; blood pressure, 162/96 mm Hg; respirations, 20 beats/min; oxygen saturation on room air, 94%. Physical examination showed an obese woman in mild respiratory distress, probable jugular veinous distention (limited assessment because of obesity), bilateral crackles on lung auscultation with good air movement, distant heart sounds with normal S1 and S2, and 2+ pitting edema to mid-shin level of both lower extremities.

An electrocardiogram showed a normal sinus rhythm with no abnormalities. It was believed that the patient was suffering from acute congestive heart failure secondary to rofecoxib. The differential diagnoses included acute myocardial infarction, pulmonary embolism, and acute valvular abnormality. It was also believed that the congestive heart failure was fairly mild and could be addressed in an outpatient setting with close monitoring. The patient was counseled to stop all NSAIDs. She was to begin the workup for this condition, and she was started on 20 mg/day furosemide. She was scheduled for laboratory work, a chest radiograph, and an echocardiogram. She was instructed that if her symptoms worsened, she was to call immediately or call 911. Close follow-up was scheduled for 2 days.

A chest radiograph (posterior/anterior and lateral) showed the heart to be at the upper limits of normal in size and had prominent vasculature suggestive of early congestive heart failure. Laboratory data revealed essentially normal serum chemistry, with sodium of 140 mEq/L (reference range, 135–146 mEq/L), potassium of 4.6 mEq/L (reference range, 3.5–5.3 mEq/L), chloride of 105 mEq/L (reference range, 98–110 mEq/L), total carbon dioxide of 24 mEq/L (reference range, 21–23 mEq/L), glucose of 111 mg/dL (reference range, 65–109 mg/dL), serum urea nitrogen of 16 mg/dL (reference range, 7–25 mg/dL), and creatinine of 0.5 mg/dL (reference range, 0.5–1.2 mg/dL). Hemoglobin was slightly low at 11.5 g/dL (reference range, 11.7–15.5 g/dL), with a mean corpuscular volume of 64.1 fL (reference range, 80–100 fL), mean corpuscular hemoglobin of 20.6 pg (reference range, 27–33 pg), mean corpuscular hemoglobin concentration of 32.2 g/dL (reference range, 32–36 g/dL), and red cell distribution width was 16.3% (reference range, 9%–15%). Her platelet count, differential, and thyroid-stimulating hormone level were normal. An echocardiogram was performed the next day. It was somewhat suboptimal because of the patient's body habitus. The left atrium was mildly dilated at 4.6 cm. The left ventricle was normal in its systolic and diastolic dimensions and wall thickness. The ejection fraction was estimated to be 63%. The aortic and mitral valves appeared normal, and the right atrium and right ventricle appeared normal. There was no pericardial effusion or thickening.

On the follow-up visit 2 days later, the patient reported heavy diuresis with resolution of her dyspnea. There was a weight loss of more than 5 pounds. Her crackles resolved as well as her jugular venous distension. The patient's furosemide was discontinued, and she returned to her normal state of health. This case was reported to the Food and Drug Administration as an adverse event.

## Discussion

NSAIDs have been widely prescribed for chronic pain and represent first-line pharmacotherapy for many inflammatory conditions. Because of undifferentiated inhibition of the cyclooxygenase enzyme by NSAIDs, various adverse effects may occur. Because of their pronounced effect on renal perfusion and renal prostaglandins, elevations in blood pressure and incidence of edema are possible in patients on NSAID therapy.[8] COX-2 inhibitors were initially believed to have renal-sparing effects, thus creating a safer renal profile than traditional NSAIDs.[10] We report the case of a patient that suffered acute congestive heart failure secondary to taking the COX-2 inhibitor rofecoxib. This case was impressive in that the patient was not suffering symptoms of congestive heart failure before initiation of the rofecoxib and experienced quick reso-

lution of the heart failure symptoms after its discontinuation. Explanations for this occurrence are offered in this discussion.

Various NSAIDs are known to affect ambulatory blood pressure in patients, some more than others.[16] Initially, the COX-2 inhibitors had not readily been associated with enhanced negative renal effects in clinical trials.[13,17] Even during initial postmarketing analysis, there was not a large incidence of edema or hypertension associated with the COX-2 inhibitors.[18] In our case, the patient was prescribed rofecoxib and developed edema and acute CHF symptoms. The patient did not experience CHF symptoms when prescribed the rofecoxib at 25 mg/day. Only after the dose was increased to 50 mg/day did the patient become symptomatic. This reveals specific characteristics about the nature of the activity of rofecoxib in relation to elimination pharmacodynamics and subsequent activity on renal function.

Currently, 3 COX-2 inhibitors are available: celecoxib, rofecoxib, and valdecoxib. Although all 3 agents meet the threshold of being classified as COX-2–specific (significant physiologic inhibition of COX-2 isoenzyme over COX-1), some differences exist among the agents. The steady-state half-life of rofecoxib is approximately 17 hours, compared with 11 hours for celecoxib. Rofecoxib seems to undergo nonlinear elimination pharmacodynamics, suggesting a possibility of accumulation of the drug in plasma concentrations.[19] Celecoxib does not seem to exhibit similar properties.[20] For persons with impaired or diminished renal function, adverse effects associated with both rofecoxib and celecoxib may lead to negative cardiorenal effects (fluid retention, edema, and hypertension). Package labeling for both agents currently issues a warning for patients with renal impairment or advanced renal disease.[19,20] However, in a study by Whelton et al, [21] a significantly greater number of patients experienced edema and hypertension while taking rofecoxib compared with patients taking celecoxib. This study is significant because it closely resembled the actual clinical uses of both medications with respect to patient populations and prescribed dosages. It was also noted in this study that management of edema was very important in restabilizing control of blood pressure.

After 2 days of loop diuretic therapy and discontinuation of the rofecoxib, the patient reported significant improvements in her symptoms. Various reports and studies have shown the ability of NSAIDs to negatively affect blood pressure.[16,22,23] Rofecoxib seems to be associated with a higher incidence of cardiorenal adverse effects compared with celecoxib[21,24,25]. However, other reports show no significant differences in the cardiorenal adverse effect profile of rofecoxib compared with celecoxib or other NSAIDs.[26,27] After a review of available literature, and clinical discussion, it was decided that increasing the dose of the rofecoxib to 50 mg, after having been previously treated at the 25-mg dose, was the likely cause of the acute CHF. In the rofecoxib package insert, it is clearly stated that the 50-mg dose was associated with a higher incidence of adverse effects, including cardiorenal effects, than the 2 lower doses (12.5 and 25 mg) Furthermore, the package insert for rofecoxib does not recommend the 50-mg dose for longer than 5 days. Some patients may not tolerate increasing the dose up to 50 mg after previous use at the lower doses.

In our patient, a history of sleep apnea increased the risk for pulmonary hypertension. She also had a history of hypertension, placing her at risk for development of left ventricular hypertrophy. Both of these factors placed this patient at risk for gradual onset of CHF but not for acute CHF. Further, the patient had no evidence of acute myocardial infarction or pulmonary embolism. Recognition of various comorbidities (age, obesity, diabetes mellitus, cardiac abnormalities, etc) by the primary care physician may play the most significant role in preventing adverse effects associated with COX-2 inhibitors. However, although these adverse effects may be observed in patients, it should be noted that not all patients would be susceptible to increased edema or blood pressure.

Several possible mechanisms have been offered to explain the adverse effects observed with the COX-2 inhibitors and more specifically rofecoxib. Possible differences in effects on sodium retention, decreased prostaglandin production, and resistance to the natriuretic effects of diuretics are all plausible causes of the development of acute edema in patients, possibly causing the acute congestive heart failure. Each of the aforementioned conditions may be successfully treated with discontinuation of the offending agent and addition of a loop diuretic. Physicians should be aware that these adverse effects may not necessarily be associated with a "class effect" of the COX-2 inhibitors. The 3 COX-2 inhibitors currently available in the United

States are chemically distinct entities with respect to their pharmacokinetic, pharmacodynamic, and COX-2–inhibiting profiles, rendering unique characteristics with respect to their efficacy and adverse effect profiles. Although the longer half-life of rofecoxib may produce some clinical benefit with respect to analgesia and anti-inflammatory properties (as yet unproven), the possible accumulation of the medication may produce untoward effects in patients. And although many NSAIDs are associated with edema and hypertension, they may not be equal in their overall incidence.[16] Particular attention should be paid to published case reports and drug labeling changes issued by the FDA or the parent company, so that recognition of differences between drugs within a drug class may be identified and applied clinically by physicians.[28]

## Conclusion

Although it is well-known and documented in the current literature that NSAID therapy, including the COX-2 inhibitors, may induce edema and hypertension in patients, the primary care physician must especially be aware of the potential for these occurrences, because it is likely that the same physician will subsequently manage the patient's declining cardiorenal status after its induction. Quick recognition of medication-induced acute congestive heart failure produced a desired outcome, avoiding hospitalization of the patient. Proper patient selection, recognition of possible pre-existing comorbidities, and prudent monitoring after medication initiations are the keys to successful patient outcomes.

## References


1. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. Am J Med 1998;105: 31S–38S.
2. Ko D, Wang Y, Berger AK, Radford MJ, Krumholz HM. Nonsteroidal antiinflammatory drugs after acute myocardial infarction. Am Heart J 2002;143: 475–81.
3. Stables G, Lawrence CM. Management of patients taking anticoagulant, aspirin, non-steroidal anti-inflammatory and other anti-platelet drugs undergoing dermatological surgery. Clin Exp Dermatol 2002;27:432–5.
4. Knijff-Dutmer EA, Kalsbeek-Batenburg EM, Koerts J, van de Laar MA. Platelet function is inhibited by non-selective non-steroidal anti-inflammatory drugs but not by cyclo-oxygenase-2-selective inhibitors in patients with rheumatoid arthritis. Rheumatology (Oxford) 2002;41:458–61.
5. Hernandez-Diaz S, Garcia-Rodriguez LA. Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. Am J Med 2001; 110 Suppl 3A:20S–27S.
6. Thatte L, Vaamonde CA. Drug-induced nephrotoxicity: the crucial role of risk factors. Postgrad Med 1996;100:83–4.
7. Murray MD, Brater DC. Renal toxicity of the nonsteroidal anti-inflammatory drugs. Annu Rev Pharmacol Toxicol 1993;33:435–65.
8. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med 1999;106:13S–24S.
9. Patrono C, Dunn MJ. The clinical significance of inhibition of renal prostaglandin synthesis. Kidney Int 1987;32:1–12.
10. Perazella MA. COX-2 inhibitors and the kidney. Hosp Pract (Off Ed) 2001;36:43–6, 55–6.
11. Perazella MA, Eras J. Are selective COX-2 inhibitors nephrotoxic? Am J Kidney Dis 2000;35:937–40.
12. LeLorier J, Bombardier C, Burgess E, et al. Practical considerations for the use of nonsteroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors in hypertension and kidney disease. Can J Cardiol 2002;18:1301–8.
13. 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. Celecoxib Long-term Arthritis Safety Study. JAMA 2000;284:1247–55.
14. Whelton A, Maurath CJ, Verburg KM, Geis GS. Renal safety and tolerability of celecoxib, a novel cyclooxygenase-2 inhibitor [published erratum appears in Am J Ther 2000;7:341]. Am J Ther 2000;7: 159–75.
15. Ahmad SR, Kortepeter C, Brinker A, Chen M, Beitz J. Renal failure associated with the use of celecoxib and rofecoxib. Drug Safety 2002;25:537–44.
16. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994;121:289–300.
17. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000;343: 1520–8.
18. FitzGerald GA, Patrono C, The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001; 345:433–42.
19. Rofecoxib package insert. Whitehouse Station (NJ): Merck & Co.; 2002.
20. Celecoxib package insert. New York: Pfizer; 2002.
21. Whelton A, Fort JG, Puma JA, et al. Cyclooxygenase-2–specific inhibitors and cardiorenal func-

tion: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients [published erratum appears in Am J Ther 2001;8:220]. Am J Ther 2001;8:85–95.

22. Curhan GC, Willett WC, Rosner B, Stampfer MJ. Frequency of analgesic use and risk of hypertension in younger women. Arch Intern Med 2002;162: 2204–8.
23. Kozuh JL. NSAIDs & antihypertensives: an unhappy union. Am J Nurs 2000;100:40–2; quiz 43.
24. Whelton A, White WB, Bello AE, et al. Effects of celecoxib and rofecoxib on blood pressure and edema in patients ≥65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol 2002; 90:959–63.
25. Zhao SZ, Reynolds MW, Lejkowith J, Whelton A, Arellano FM. A comparison of renal-related adverse drug reactions between rofecoxib and celecoxib, based on the World Health Organization/Uppsala Monitoring Centre safety database. Clin Ther 2001; 23:1478–91.
26. Gertz BJ, Krupa D, Bolognese JA, Sperling RS, Reicin A. A comparison of adverse renovascular experiences among osteoarthritis patients treated with rofecoxib and comparator non-selective nonsteroidal anti-inflammatory agents. Curr Med Res Opin 2002;18:82–91.
27. Frishman WH. Effects of nonsteroidal anti-inflammatory drug therapy on blood pressure and peripheral edema. Am J Cardiol 2002;89:18D–25D.
28. Woosley RL. Drug labeling revisions—guaranteed to fail? JAMA 2000;284:3047–9.