Reversible and Irreversible Pulmonary Toxicity Associated with Cyclooxygenase-2 Inhibitors

John K. S. Chia, MD*
John A. Ohara, MD†
Michael N. Nakata, MD*
Robert S. Y. Chang, MD*

*Department of Medicine
†Department of Pathology
Little Company of Mary Hospital, Torrance, California

KEY WORDS: Cox-2 inhibitor, pulmonary toxicity, fibrosis

ABSTRACT

Cyclooxygenase-2 (COX-2) inhibitors are safe medications widely prescribed for pain and arthritis. Recently, we evaluated a number of patients who developed severe dyspnea, some with irreversible lung damage, while taking COX-2 inhibitors. No other obvious etiologies were found after extensive evaluation. The possible mechanism of an uncontrolled inflammatory process with fibrosis as the result of inhibition of COX-2 is discussed based on available research data.

INTRODUCTION

Selective cyclooxygenase-2 (COX-2) inhibitors have become a popular treatment for a variety of arthritic conditions. Over a 12-month period, we have seen several patients who developed unexplained dyspnea with or without severe pulmonary infiltrates/fibrosis and hypoxemia while taking COX-2 inhibitors. We present case studies of four of these patients; 2 patients died despite aggressive supportive care and high-dose steroids.

CASE REPORTS

Case 1

An 83-year-old white female developed significant knee arthritis, which responded to the administration of 25 mg rofecoxib (Vioxx) per day. Two months after the start of treatment, the patient developed marked dyspnea without edema, weight gain, or any other associated symptoms, and was unable to walk more than 10 feet. The results of chest x-ray, ventilation–perfusion scan, 2-dimensional echocardiogram, and Persantine Cardiolyte stress test were normal except for mildly elevated pulmonary artery pressure (35 mm Hg). Pulmonary function test showed no significant abnormality except for diffusing capacity of lung for carbon monoxide (Dlco) of 76%. (ANA) titer was 1:640 with a homogeneous pattern(normal <1:40) but the sedimentation rate was normal. The symptoms resolved within 2 weeks of discontinuation of medication. Dlco and ANA titer did not change significantly at 1-year follow up. The patient was not rechallenged with the medication.

Case 2

A 53-year-old male ex-heroin abuser with known hepatitis C was given celecoxib

(Celebrex) for lower back pain. Within 2 months of drug administration, he developed progressive dyspnea without fevers, cough, or chest pain. The patient was admitted to the hospital for severe hypoxemia, and the chest x-ray revealed diffuse interstitial infiltrates. The patient failed to respond to 100% O_2, trimethoprim/sulfamethoxazole and levofloxacin (Levaquin). One week later, an open lung biopsy showed organizing lung injury with airspace fibrin and reactive pneumocytes. The interstitium was markedly thickened and fibrotic in some areas. Refractile bodies were seen in histiocytes scattered around the interstitium. Special stains and cultures found no evidence of infection. The patient was treated with high-dose steroids, which resulted in slow improvement of the oxygen exchange. He was discharged 6 weeks later on tapering steroid dosage. The patient was taken off steroids after 4 months of therapy. Eight months later, he continued to have dyspnea after walking 2 blocks but no longer needed oxygen. His chest x-ray still showed residual interstitial changes.

Case 3

A 79-year-old Japanese American female without any prior medical problems developed progressive dyspnea approximately 2 months after taking rofecoxib for arthritic pain. She had a minimal, nonproductive cough but did not have any fevers or flu-like symptoms. The dyspnea worsened markedly approximately 3 months after the start of therapy, requiring admission to the hospital. Her chest x-ray showed severe, bilateral pulmonary infiltrates. High-resolution computed tomography scan of the chest demonstrated a coarse interstitial process with marked septal lobular and intralobular thickening in upper and lower lung zones. She required mechanical ventilation, 100% oxygen, and high levels of positive end-expiratory pressure for severe hypoxemia. Tracheal secretions were negative for bacterial pathogens, *Legionella, Mycobacterium*, fungus, viruses, and *Pneumocystis*. Despite treatment with moxifloxacin (Avelox), trimethoprim/sulfamethoxazole, high-dose steroids, and gamma interferon, the lung disease worsened and the patient died approximately 1 month later. No autopsy was obtained.

Case 4

An 81-year-old woman with a history of breast carcinoma, stage T2N1M0 in 1997, which had been treated with total mastectomy and chronic tamoxifen therapy, developed significant progressive dyspnea 1.5 months before admission. She had been taking celecoxib on and off for approximately 10 months before the onset of the dyspnea. She switched to naproxen for 1 month soon after the dyspnea started. Cardiac evaluation, including a Persantine Cardiolyte stress test and 2-dimensional echocardiogram, was normal. One week after resuming celecoxib, she developed a marked increase in dyspnea along with minimal nonproductive cough but did not have fevers or flu-like symptoms. Her chest x-ray showed bilateral infiltrates, which progressed to complete "white-out" of both lungs within 2 to 3 days of admission. Extensive workup for infectious agents was negative, and the patient failed to improve despite antibiotics, high-dose steroids, and mechanical ventilation. Therapy was eventually withdrawn after 10 days of hospitalization. Autopsy of the lung showed acute and organizing diffuse alveolar damage with areas of hyaline membrane formation, squamous metaplastic cells lining intraalveolar space, interstitial fibrosis, and chronic interstitial inflammation. Numerous type 2 pneumocytes with reactive changes and prominent macrophages were found in the air spaces with some background scarring in some sections. Four right peribronchial lymph nodes had microscopic evidence of metastatic breast carcinoma; there was no evidence of metastatic carcinoma of the lung tissue.

DISCUSSION

These case reports on drug-related toxicity do not necessarily prove causality and could

merely represent rare association with widely prescribed drugs. However, drug-induced toxicity, whether direct or indirect, is a plausible explanation in these cases because other causes were excluded by process of elimination. None of the patients had fevers or other signs of infections before admission; no evidence of infections was found after extensive laboratory evaluation and examination of the lung tissues. One could not exclude the possibility of a viral infection triggering the inflammatory process. In the *Physician Desk Reference*, dyspnea and pneumonia are mentioned as adverse drug reaction to the previously mentioned drugs, yet there is a paucity of report published in the literature.[1]

It appears that COX-2 inhibitors can cause reversible dyspnea, as in case 1 and in other patients we have seen in the clinics who were not worked up adequately to be included in this report). The mild decrease of DLco and absence of hypoxemia in our patient did not seem to explain her profound symptomatology. Furthermore, there was no significant obstructive changes documented by the pulmonary function test. The symptoms resolved within 2 weeks of stopping the medication. The presence of antinuclear antibodies could suggest a possible immunologic mechanism for reversible lung toxicity.

On the other hand, severe lung toxicity, irreversible in some, was observed in the other patients included in this report. Pathologic examination of lung tissues from patients 2 and 4 showed significant interstitial inflammation and evidence of fibrosis along with acute organizing lung injury. None of the patients had obvious evidence of infections by cultures, special stains, and serologies, and none were on any other drugs known to cause pulmonary toxicity. The process gradually improved in patient 2 with steroid treatment over a period of several months. However, he continued to have dyspnea on exertion but was no longer oxygen-dependent for ambulation. The chest x-ray continues to show residual infiltrates.

COX-2 has been implicated as an important mediator of pulmonary fibrosis.[2] Mice deficient in the COX-2 gene (COX-2 -/-) are known to develop severe pulmonary fibrosis. In wild-type and Cox-1 -/- mice, COX-2 protein is induced in Clara cells of terminal bronchioles when exposed to vanadium pentoxide (vp) and the level of PGE_2 is upregulated. COX-2 -/- mice failed to upregulate PGE_2 production on exposure to vp; tumor necrosis factor levels in bronchoalveolar fluid remained chronically and significantly elevated, as compared with that of the wild-type or Cox-1 -/- mice.[2] Decrease in suppressive PGE_2 is associated with increased fibroblast proliferation, which contributes to the propensity for pulmonary fibrosis.[3] Patients with idiopathic pulmonary fibrosis are thought to have a deficiency in COX-2 gene expression.[4] Some researchers are currently contemplating COX-2 gene replacement therapy for patients with idiopathic pulmonary fibrosis.[5] Ironically, the use of COX-2 inhibitor could actually create an acquired form of COX-2 deficiency.

Clara cells in the terminal bronchioles of human and other animals are known to have high-affinity binding receptor for the methanesulfonate moiety of chemicals such as polychlorinated biphenyl,[6,7] a side group found in rofecoxib as well as busulfan (Myleran, Bulsulfex), the latter known to have significant lung toxicity.[8] Chemicals with this specific moiety are likely concentrated in the Clara cells, and toxicity can occur by different mechanisms. If Clara cells are predominantly involved in the regulation of inflammation through the induction of the COX-2 gene and production of regulatory prostanoids for control of inflammation, it is conceivable that inhibition of such process by the COX-2 inhibitors could predispose to uncontrolled inflammation and fibrinogenesis when a minor stimulus such as viral infection occurs.

Taken together, these rare clinical observations of pulmonary toxicity in patients taking COX-2 inhibitors are supported by

the mechanisms elucidated by basic science research. More work is needed to define the true prevalence, genetic predisposition, triggering event, and the cause–effect relationship of drug-related toxicity. Until further information becomes available, one needs to have heightened awareness of possible pulmonary toxicity associated with the use of COX-2 inhibitors when dyspnea occurs during treatment.

ACKNOWLEDGMENT

This work is supported by the Chu-Lee Tu memorial research fund.

REFERENCES

1. Mehandru S, Smith RL, Sidhu GS, Cassai N, Aranda CP. Migratory pulmonary infiltrates in a patient with rheumatoid arthritis. *Thorax.* 2002;57:465–467.
2. Bonner JC, Rice AB, Ingram JL, et al. Susceptibility of cyclooxygenase-2 deficient mice to pulmonary fibrogenesis. *Am J Pathol.* 2002;161:459–470.
3. Lama V, Moore BB, Christensen P, Toews GB, Peters-Golden M. Prostaglandin E2 synthesis and suppression of fibroblast proliferation by alveolar epithelial cells is cyclooxygenase-2-dependent. *Am J Respir Cell Mol Biol.* 2002;27:752–758,
4. Wilborn J, Crofford LJ, Burdick MD, et al. Cultured lung fibroblasts isolated from patients with idiopathic pulmonary fibrosis have a diminished capacity to synthesized prostaglandin E2 and to express cyclooxygenase-2. *J Clin Invest.* 1995;95:1861–1868.
5. Jenkins G, Hart L, Hodges R, et al: Cyclooxygenase-2 over expression, using an integrin-targeted gene delivery system (the LID vector), inhibits fibroblast proliferation in vitro and leads to increased prostaglandin E2 in the lung. *Chest* 2002;121:102S–104S.
6. Lund J, Anderson O, Poellinger L, Gustafsson JA. In vitro characterization of possible mechanisms underlying the selective in vivo accumulation of the PCB metabolite 4, 4'-bis (methylsulphonyl-2,2',5,5'-tetrachlorobiphenyl in the lung. *Food Chem Toxicol.* 1986;24:563–566.
7. Lund J, Nordlund L, Gustafsson JA. Partial purification of a binding protein for polychlorinated biphenyls from rat lung cytosol: physicochemical and immunochemical characterization. *Biochemistry.* 1988;27:7895–7901.
8. Vergnon JM, Boumcheron S, Riffat J, Guy C, Blanc P, Emonot A. Interstitial pneumopathies caused by busulfan. Histologic, developmental and bronchoalveolar lavage analysis of 3 cases. *Rev Med Interne.* 1988;9:377–383.