Sulfasalazine-induced Pulmonary Disease*

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We report the findings in two patients with sulfasalazine-induced pulmonary disease. The first patient developed pulmonary interstitial fibrosis after more than 4 yr of treatment for Crohn's disease. Pulmonary symptoms and chest roentgenographic and pulmonary function abnormalities gradually reversed after stopping the drug. No specific treatment was given. The second patient, who had rheumatoid arthritis without pulmonary disease, received the drug for 1 yr without experiencing any problems. Readministration seven months later resulted in the development of an acute interstitial pulmonary disease. Discontinuing the drug and treatment with corticosteroids produced rapid improvement. We discuss these patients in relation to other reports of sulfasalazine-induced pulmonary toxicity, highlighting their atypical features. (Chest 1992; 101:1033-37)

Sulfasalazine has been widely used in the treatment of inflammatory bowel disease for over 40 yr and more recently for the treatment of other inflammatory conditions. The most common side effects are gastrointestinal disturbances, anorexia, headache, arthralgias, skin rashes, hemolytic anemia, leukopenia, and hepatitis. Pulmonary toxicity is rare. There have been only 19 cases reported in the English literature through 1988. We report two additional cases of sulfasalazine-induced pulmonary disease with different manifestations. The first is a patient with pulmonary interstitial fibrosis which developed after more than 4 yr of continuous treatment, was not associated with eosinophilia, and reversed with cessation of the drug and without further therapy. The second patient developed acute interstitial pneumonitis shortly after reintroduction of the drug, which reversed rapidly following discontinuing the drug and treatment with corticosteroids.

CASE REPORTS

CASE 1

A 69-yr-old businessman without any known occupational exposure

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<table>
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<th>Table 1—Pulmonary Function Data for Patient 1*</th>
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<td><strong>Data</strong></td>
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<td>PaO₂, mm Hg</td>
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<td>Oxygen saturation, percent</td>
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*Numbers within parentheses represent percentage of predicted value.
counts, normal differential count, an erythrocyte sedimentation rate of 40 mm/h, normal findings on urinalysis, and normal results of automated blood analysis (SMA-20). Multiple cultures obtained from sputum, blood, and urine were all negative. Arterial blood gas analysis revealed pH of 7.48, PaCO₂ of 37 mm Hg, and PaO₂ of 58 mm Hg while breathing 35 percent oxygen by face mask. A chest x-ray film revealed bilateral interstitial infiltrates, much more extensive than those present 6 mo earlier (Fig 1B). Fiberoptic bronchoscopy, including transbronchial biopsy, failed to reveal any abnormalities. Washings and brushings were negative for microorganisms and malignant cells. Pulmonary function tests revealed a moderate reduction of lung volumes (Table 1). An open lung biopsy was performed on Aug 22, 1989. Specimens obtained from the left upper and lower lobes showed patchy areas of interstitial fibrosis, intra-alveolar organizing infiltrate, and macrophage infiltration consistent with usual interstitial pneumonitis (Fig 2). There was no evidence of bronchiolitis obliterans or large numbers of eosinophils.

The patient was discharged on Sept 1, 1989. The plan was to allow the thoracotomy incision to heal and then initiate prednisone therapy. He was seen in the office on Sept 12, 1989, feeling much better and with improved pulmonary function (Table 1). It was decided not to start the prednisone. Over the next several months the patient’s condition continued to improve symptomatically. Pulmonary function tests and arterial blood gas levels normalized except for the reduced diffusing capacity (Table 1). At the time of the patient’s last visit in April, 1990, he had returned to his premorbid state and a chest x-ray film showed nearly complete clearing (Fig 1C). In the absence of sulfasalazine and while the pulmonary disease improved, the patient’s inflammatory bowel disease worsened; however, the sulfasalazine was not restarted, and his condition was managed with other agents.

CASE 2

A 74-yr-old Japanese woman had a long history of rheumatoid arthritis. She was treated with sulfasalazine 500 mg twice daily for 1 yr. It was discontinued on May 19, 1989 because of worsening arthritis. Methotrexate (5 to 7.5 mg orally per week) was given instead. After initial improvement the arthritis worsened, and sulfasalazine at 500 mg twice daily was restarted on Dec 15, 1989. The patient presented to Northwestern Memorial Hospital on Dec 18, 1989 with a two-day history of fever and a nonproductive cough, but no shortness of breath. She appeared moderately ill with a pulse rate of 104 beats per minute, blood pressure of 95/55 mm Hg, respiration rate of 30/min, and temperature of 38.0°C. New inspiratory crackles were present over the lower half of both lungs. Findings from the remainder of the physical examination were normal except for joint abnormalities consistent with rheumatoid arthritis. Results of laboratory tests included normal red and white blood cell counts and normal differential count (no eosinophilia). Arterial blood gas analysis revealed pH of 7.53, PaCO₂ of 26 mm Hg, and PaO₂ of 46 mm Hg while breathing room air; and pH of 7.53, PaCO₂ of 26 mm Hg, and PaO₂ of 51 mm Hg while breathing 50 percent oxygen by face mask. A chest x-ray film revealed bilateral interstitial infiltrates, which were greater at the bases. Multiple cultures of sputum, blood, and urine were negative. The methotrexate and sulfasalazine were discontinued, and the patient received broad-spectrum antibiotics; however, her condition worsened, and she required intubation and mechanical ventilation. Fiberoptic bronchoscopy failed to reveal a diagnosis. An open lung

FIGURE 1. Chest x-ray films taken before (A), during (B), and after resolution (C) of patient’s illness. A (top): February 1989; during admission for aortofemoral bypass surgery. There are fine bilateral infiltrates. B (middle): August 1989; during admission to Northwestern Memorial Hospital for interstitial pulmonary disease. Extensive bilateral interstitial infiltrates are present. C (bottom): April 1990, eight months after stopping sulfasalazine. Chest x-ray film is normal.
biopsy was performed on the fifth day of hospitalization. Tissue obtained from the right lower lobe revealed acute interstitial pneumonitis with abundant alveolar macrophages, minimal interstitial thickening, and no evidence of granulomas, eosinophils, microorganisms, or bronchiolitis. The patient was started on methylprednisolone (20 mg every 6 h) and her condition improved rapidly. Within two days of corticosteroid treatment, she was weaned from the ventilator and required only low-dose oxygen by nasal cannula. She was discharged eight days after the open lung biopsy, feeling much improved; the chest x-ray film showed resolving infiltrates; and arterial blood gas analysis on room air revealed pH of 7.52, PaCO₂ of 35 mm Hg, and PaO₂ of 67 mm Hg. The corticosteroids were slowly tapered over the next several weeks, and the patient remained free of respiratory symptoms.

**Discussion**

Sulfasalazine is a poorly absorbed sulfonamide used to treat inflammatory bowel disease and other inflammatory processes. The incidence of pulmonary reactions due to sulfasalazine appears to be low. Jones and Malone1 in 1972 were the first to report a case of pulmonary eosinophilia which they attributed to sulfasalazine. Since then, 18 other cases have been reported.1-17

The pulmonary response to sulfasalazine appears to be limited. A few distinct clinical syndromes have been described, including hypersensitivity pneumonitis, diffuse interstitial fibrosis,3,8,10,11 bronchiolitis obliterans,8,15 and tracheal laryngitis with bronchospasm.1 Hypersensitivity pneumonitis, which is thought to represent an immunologic response to a number of agents including drugs, is the most common.16 Sulfasalazine is metabolized in the bowel to 5-aminosalicylic acid (5-ASA), which is the active therapeutic agent, and sulfapyridine, which transports 5-ASA to the colon.17 The sulfapyridine moiety is thought to be responsible for the toxicity. In one report a patient developed eosinophilic pneumonia while being treated with sulfasalazine and improved when the drug was stopped; however, when rechallenged with sulfapyridine, symptoms recurred. Subsequently, the patient was treated with olsalazine, a 5-ASA compound, without recurrence of pulmonary symptoms.17

Clinical features of hypersensitivity pneumonitis due to sulfasalazine include cough, dyspnea, fever, pulmonary infiltrates which are usually patchy and bilateral, and peripheral blood eosinophilia, which is present in most but not all patients.1,3,14 In one patient who was rechallenged with the drug, symptoms recurred, but the eosinophil count remained normal.1 Symptoms usually develop between 1 and 6 mo after starting sulfasalazine and quickly resolve when the drug is stopped; however, there have been two deaths despite stopping therapy.3,11

The dose of sulfasalazine associated with the development of pulmonary disease is usually between 4 and 6 g daily. The most common pulmonary function test abnormality is a reduced Dco. Furthermore, a reduction in the Dco has been reported after rechallenge with sulfasalazine.4 An obstructive pattern has also been described in some patients.4,5,10 A tissue diagnosis was obtained in three patients; two had a transbronchial biopsy,12,14 and one had an open lung biopsy.15 The histopathologic findings included interstitial pneumonitis and slight fibrosis but no tissue eosinophilia.12,14 There was associated bronchiolitis obliterans in one patient.15

The other pulmonary syndromes associated with sulfasalazine are less frequent. They are considered by some authors to be a subset of hypersensitivity pneumonitis because they have similar signs and symptoms and they are commonly associated with fever and peripheral eosinophilia.10

The prognosis of patients who develop sulfasalazine-induced pulmonary disease is generally good. Most patients rapidly improve symptomatically with stopping the drug. Their pulmonary function also rapidly becomes normal, although the Dco may take longer to recover; however, two patients died in spite of stopping the sulfasalazine. One had fibrosing alveolitis on postmortem examination;2 the other had fibrosis without a significant inflammatory response.11 Although there is some suggestion that corticosteroids may speed recovery, and they may have done that in our second patient, most patients appear to recover at about the same rate whether or not corticosteroids are used.

Risk factors for any of the syndromes associated with sulfasalazine therapy are unclear. No studies, either clinical or using animal models, have identified a specific mechanism by which sulfasalazine induces pulmonary disease. Two patients with known salicylate hypersensitivity2,5 and one with a previous allergy to sulfonamides12 developed pulmonary disease while taking sulfasalazine. Seven patients were rechallenged with sulfasalazine, and symptoms and pulmonary infiltrates recurred in all of them.2,4,5,7,10,15,17

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exhibited a skin reaction to sulfasalazine, for which he received desensitization treatment with the drug. After restarting the drug, the skin reaction did not recur, but an acute pneumonitis developed 2 mo later. There is only one report of an unsuccessful attempt to desensitize a patient with sulfasalazine-induced pulmonary disease.\(^{14}\) The wisdom of such an approach is unclear.

Our first patient had chronic interstitial pneumonitis with fibrosis (fibrosing alveolitis) which differed from those previously reported in several major aspects. First, he had received the drug continuously for nearly 5 yr before developing significant pulmonary symptoms. This is only the second report of pulmonary toxicity after such a long exposure to the drug. The first had a duration of exposure of 6 yr.\(^{16}\) Prior to that report, the longest duration of exposure was 36 mo.\(^{6}\) In all other reports the duration was between 1 and 6 mo. Secondly, he presented with diffuse interstitial pneumonitis confirmed by open lung biopsy and no evidence of a hypersensitivity reaction, although he did have pleural fluid eosinophilia. Thirdly, the patient's condition improved following withdrawal of the drug, in the absence of treatment with corticosteroids.

Pulmonary complications due to inflammatory bowel disease have been reported. They include pulmonary vasculitis,\(^{20}\) chronic bronchial suppuration and bronchiectasis,\(^{21,22}\) an isolated reduction in the DCQ,\(^{23}\) and interstitial pulmonary fibrosis;\(^{24}\) however, our first patient's pulmonary disease is unlikely to be due to inflammatory bowel disease because his bowel disease was stable when the pulmonary disease developed, the bowel disease worsened after the sulfasalazine was stopped, and there was a strong relationship between withdrawal of the drug and subsequent symptomatic and objective improvement of his pulmonary disease.

The second patient had a different presentation, one consistent with an acute pulmonary interstitial reaction. In contrast to the first patient, it is more difficult to be absolutely certain that her pulmonary disease was due to sulfasalazine, since rheumatoid arthritis and methotrexate both produce pulmonary disease. Pulmonary manifestations of rheumatoid arthritis include necrotic nodules, pleural effusions, obliterative bronchiolitis, and fibrosing alveolitis.\(^{25}\) Fibrosing alveolitis usually presents in an indolent fashion, and clubbing is a common feature. The mean duration of joint symptoms before the development of pulmonary disease is approximately 5 yr. The response to corticosteroids is fair at best, and mortality exceeds 50 percent at 5 yr.\(^{25}\) It is unlikely that our patient's pulmonary disease was due to rheumatoid arthritis because of the acute onset, the prolonged duration of joint disease before development of the pulmonary disease, differences in pathology, and the excellent response to corticosteroid treatment.

The incidence of pulmonary toxicity due to low-dose methotrexate in patients with rheumatoid arthritis appears to be low (approximately 5 percent).\(^{20,27}\) The clinical presentation is usually subacute, with shortness of breath, nonproductive cough, and fever. Pathologic changes include a hypersensitivity reaction with interstitial pneumonitis, granuloma formation, bronchiolitis, and diffuse alveolar damage.\(^{27}\) There does not appear to be any correlation between toxicity and the dose or duration of treatment. It is unlikely that the pulmonary disease in our patient was due to methotrexate, since it occurred in proximity to restarting treatment with sulfasalazine, while the dose of methotrexate remained constant, the onset was very rapid, and there was no clinical evidence of pulmonary disease before the sulfasalazine was begun.

The absence of peripheral blood and lung eosinophilia in both patients cannot be explained; however, this is not an unusual finding in drug-induced pulmonary disease, where only 40 percent or so of the patients have peripheral eosinophilia.\(^{18}\) Furthermore, 25 percent of the patients with sulfasalazine-induced pulmonary disease have been reported not to have eosinophilia.

Although rechallenge with the drug and redevelopment of disease would have strengthened the diagnosis in both patients, especially the second patient, we were reluctant to do this because the pulmonary disease was severe at the time of presentation.

In summary, we have presented the findings in two new patients with sulfasalazine-induced pulmonary disease who had several atypical features, and we have reviewed the earlier literature. Sulfasalazine-induced pulmonary disease, although rare, has varying presentations, as illustrated by our patients, and is an important complication to recognize in view of the potential for permanent lung damage and even death. Prompt recognition of the disease, even when the drug has been ingested for years and symptoms have been present for months, followed by immediate cessation of the drug, should result in an excellent prognosis.

**References**


Sulfasalazine-induced Pulmonary Disease (Hamadeh, Atkinson, Smith)
10 Sigvaldason A, Sorenson S. Interstitial pneumonia due to sulfasalazine. Eur J Respir Dis 1983; 64:229-33

1992 Spoleto Pulmonary Symposium

The American College of Chest Physicians, the Medical University of South Carolina, and Ohio State University will present this program at the Omni Hotel at Charleston Place, Charleston, South Carolina, June 4-5. For information, contact the Division of Education, ACCP, 3300 Dundee Road, Northbrook, IL 60062 (708:498-1400).