Ticlopidine-Induced Interstitial Pulmonary Disease*

A Case Report

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We report a case of interstitial pulmonary disease that occurred together with lymphocytic colitis during treatment with ticlopidine. The drug was prescribed for transient ischemic cerebrovascular accidents. Ticlopidine treatment was stopped, and a prolonged course of prednisone was necessary to treat the pulmonary and intestinal symptoms. So far, few cases of pulmonary side effects caused by ticlopidine have been reported. This case is unique in that interstitial lung disease evolved in parallel with colitis and caused severe hypoxemia. Special care should be taken when pulmonary symptoms appear in association with ticlopidine treatment.

(CHEST 2001; 119:1963–1965)

Key words: collagenous colitis; eosinophilic pneumonia; interstitial pulmonary disease; lymphocytic colitis; ticlopidine

Ticlopidine is an inhibitor of platelet activation. It inhibits the adenosine diphosphate receptors of the platelet and thus prevents partial platelet attachment. Many randomized studies with ticlopidine have shown a reduction of stenosis in stents after percutaneous transluminal coronary angioplasty. Its usefulness is also proven in cerebrovascular ischemic diseases. A few side effects are well known, such as neutropenia (2.4% of treated cases; of these, 0.8% are severe), thrombocytopenia, cholestatic hepatitis (rare), thrombocytic thrombocytopoietic purpura (very uncommon) and, more frequently, GI symptoms (nausea and vomiting in up to 40%). Sometimes, chronic diarrhea is associated with microscopic lymphocytic colitis.1-4 To our knowledge, no interstitial pulmonary disease has been described with ticlopidine treatment in association with diarrhea. We report herein the case of a new onset of diarrhea, followed by dyspnea and dry cough, in an old woman treated with ticlopidine for cerebrovascular transient ischemic accident (TIA).

CASE REPORT

A 79-year-old woman was treated since November 22, 1998, with aspirin and ticlopidine for recurrent TIA. No clear etiology was found for the TIA. Ticlopidine was added to the treatment because of repetitive neurologic symptoms with aspirin alone. At that time, the patient did not have any respiratory or digestive symptoms. On January 14, 1999, she was admitted to our hospital for diarrhea and progressive dyspnea. Diarrhea appeared 10 days after the introduction of ticlopidine. At the time of hospital admission, the patient had 8 to 10 watery stools per day with no blood and no abdominal pain. She had no significant weight loss and was in good general condition with no fever. Physical examination was normal, including chest and abdomen. Aspirin and ticlopidine were stopped immediately, and oxygen supplementation was administered for dyspnea. Results of bacteriologic studies of the stool, searching for the presence of blood and fat, as well as parasites, and Clostridium difficile toxin were all negative. Results of a lactose tolerance test and gastroscopy were normal. Thyroid, liver, and pancreatic function tests results as well as serum electrolytes were also normal. CBC count showed no eosinophilia (31 g/L). Results of antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, and complement C3 and C4 were all normal. A colonoscopy was performed with biopsies, showing lymphocytic colitis associated with mini-

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Arterial blood gas analysis under room air conditions showed severe hypoxemia (pH 7.46; PaO₂, 32.1 mm Hg; PaCO₂, 41.25 mm Hg). A chest radiograph revealed a diffuse, interstitial infiltrate that was not present on previous radiographs. Pulmonary function test results were compatible with a restrictive defect: FVC, 0.97 L (49% of predicted value); FEV₁, 0.82 L (51%); and FEV₁/FVC, 0.85 (105%). A thoracic CT scan confirmed the diffuse, interstitial infiltrate without lymphadenopathy or pleural effusion (Fig 1). A search for respiratory pathogens was negative. No improvement was noted with diuretic treatment. The patient underwent fiberoptic bronchoscopy with macroscopically normal findings. BAL fluid revealed 51 × 10⁴ cells/mL with 50% macrophages, 21% lymphocytes, 2% neutrophils, 24% eosinophils, 0.5% basophils, and 2.5% bronchial epithelial cells. Transbronchial lung biopsy could not be performed because the patient had difficulty tolerating the procedure.

No clinical or radiologic improvement was noted after ticlopidine treatment was stopped. Prednisone, 1 mg/kg, was administered 15 days after admission. Three days later, we noticed complete recovery from respiratory symptoms, with disappearance of the diffuse lung infiltrate on chest radiograph as well as resolution of diarrhea. Spirometry normalized after 10 days of steroid treatment, and the patient returned home. After 3 weeks, prednisone treatment was stopped, but both diarrhea and shortness of breath reappeared rapidly. Once again, the patient was administered prednisone (1 mg/kg/d with subsequent dose tapering) and her symptoms disappeared. Prednisone treatment could be stopped definitively after 4 months, and the patient has been well since then.

**Discussion**

We report a case of interstitial lung disease associated with lymphocytic and collagenous colitis that occurred after introduction of ticlopidine treatment. These manifestations resolved after withdrawal of the drug and treatment with prednisone. The recurrence of both respiratory symptoms and diarrhea at the time of an early attempt to discontinue prednisone treatment suggests that both manifestations had the same origin and were secondary to ticlopidine. Indeed, several reports in the literature have shown ticlopidine to be responsible for the development of lymphocytic and collagenous colitis. This is the first time that this side effect is reported to occur together with pulmonary involvement. The only other medication that could be incriminated is aspirin. However, the patient had taken aspirin alone before ticlopidine with no particular side effects. While nonsteroidal anti-inflammatory drugs have been reported to be a rare cause for interstitial lung disease with eosinophilia, treatments with salicylates have been mainly implicated in acute, noncardiogenic pulmonary edema. Therefore, it seems very unlikely that aspirin played a role in our case. This ticlopidine-induced interstitial lung disease was characterized by severe hypoxemia, and the chest CT scan showed a pattern of patchy ground-glass opacities together with peribronchovascular thickening (Fig 1). This aspect is consistent with that observed in hypersensitivity pneumonitis as well as in bronchiolitis obliterans and organizing pneumonia (BOOP). There was no blood eosinophilia, but there was a highly increased count of eosinophils in the BAL fluid. Because of the latter finding, differential diagnosis should also include chronic eosinophilic pneumonia and other eosinophilic lung diseases. However, the rapid onset of the symptoms, the absence of atopy, and the CT-scan pattern made the diagnosis of chronic eosinophilic pneumonia unlikely. In addition, laboratory investigations were negative for parasitic infection and collagen vascular disease. A case of BOOP caused by ticlopidine was recently reported by Alonzo-Martinez and coworkers. Because we were unable to obtain a lung biopsy, BOOP could not be formally proven in our case. The association of severe hypoxemia, ground-glass opacities, and high count of eosinophils in BAL fluid is a rare feature of BOOP, while relapse after rapid steroid taper is typical. Consequently, we conclude that BOOP, or alternatively hypersensitivity pneumonitis, represents the most likely cause for interstitial lung disease in our patient. We found four additional cases of pulmonary disease in association with ticlopidine treatment in the adverse reactions register of the World Health Organization. Unfortunately, no specific information could be obtained on these patients.

In summary, our case was remarkable in that interstitial lung disease evolved in parallel with lymphocytic colitis, caused severe hypoxemia, and warranted >3 weeks of treatment with prednisone to control. The association with lymphocytic colitis and the severity of the respiratory symptoms suggest that a profound immunologic reaction occurred. Special care should be taken when pulmonary symptoms appear in association with ticlopidine treatment.

**References**


![Figure 1. High-resolution chest CT scan (1.0-mm slice) showing diffuse, peribronchovascular interstitial thickening with patchy ground-glass opacities.](image-url)
Bilevel Nasal Positive Airway Pressure and Ballooning of the Stomach*

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We describe a case of severe gastric insufflation in a patient with amyotrophic lateral sclerosis who was receiving bilevel nasal positive airway pressure (BNPAP) ventilation (BiPAP; Respironics; Murrysville, PA). The injection of inspiratory flow into the esophagus, aerophagia, and air trapping below the gastroesophageal junction after a meal are probably the major causes. We suggest that BNPAP ventilation can be a cause of serious gastric insufflation in a patient who lies supine, especially after a meal, and attention should be paid to avoiding this complication by having the patient sit up for about half an hour after a meal.


Key words: aerophagia; amyotrophic lateral sclerosis; bilevel nasal positive airway pressure; gastric insufflation; ileus; supine position

Abbreviations: ALS = amyotrophic lateral sclerosis; BNPAP = bilevel nasal positive airway pressure

Bilevel nasal positive airway pressure (BNPAP) [BiPAP system; Respironics Inc; Murrysville, PA] is now widely used for the management of respiratory insufficiency of various causes including amyotrophic lateral sclerosis (ALS), and its complications are well-known. Gastric insufflation is observed in 30 to 50% of patients receiving noninvasive positive-pressure ventilation, but it is usually not serious.1 As far as we know, no one has reported on the potential danger of gastric insufflation in patients receiving BNPAP in the supine position, especially after a meal. We report on an unusual case in which severe gastric insufflation resulted from the injection of air into the esophagus by BNPAP and aerophagia.

CASE REPORT

A 42-year-old woman with ALS complained of gastric distension after a lunch of soup and noodles. She had been receiving BNPAP treatment for a year because of a rapid decline in respiratory function. She was using a standard nasal mask. The system had been set in the “spontaneous/timed” mode, and the inspiratory and expiratory pressures had been set at 14 and 4 cm H2O, respectively. Her cranial nerves were normal except for a slight weakness and atrophy of the tongue. She could speak, eat, and drink but could not sit up because of generalized muscle weakness, joint contracture, and pain. She repeatedly vomited, eructated, and swallowed air. Her upper abdomen was tympanic, but bowel sounds were normal. Aerophagia was diagnosed, and the patient was treated with sedatives, which soon appeared to be ineffective. Treatment with decompression by means of a nasogastric tube was rejected by the patient.

Despite continued attempts by the staff, the patient became increasingly irritable and continued to vomit and swallow air. She appeared to be difficult to synchronize with the BNPAP ventilation system. In the late afternoon, her abdomen became fairly tense and tympanic. She complained of sharp abdominal pain and respiratory distress. Her arterial oxygen saturation level also declined. A radiograph revealed a large amount of air in the stomach and an elevated diaphragm (Fig 1). A forcibly inserted nasogastric tube immediately relieved her symptoms. Her bowels

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Manuscript received July 31, 2000; revision accepted December 3, 2000.

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FIGURE 1. An abdominal radiograph showing a large amount of air in the stomach.