**REFERENCES**


**Quinidine-Induced Reversible Pneumonitis**

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We report a patient who developed fever and rapidly progressing lung infiltrates 4 days after the beginning of continuous quinidine sulfate therapy. The fever disappeared during the following 48 h and the pneumonitis slowly resolved over the next month once quinidine therapy was stopped. The diagnosis of quinidine-induced pneumonitis, which has not previously been reported in the literature (to our knowledge), was confirmed by means of a rechallenge with quinidine.

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Quinidine has a variety of side effects associated with it in man, including gastrointestinal irritation, cardiovascular toxicity, and hypersensitivity reactions such as hepatitis, blood dyscrasias (particularly thrombocytopenia), rash, and fever. Quinidine fever, a rare manifestation of toxicity or sensitivity to the drug, has been known since 1922, but to the best of our knowledge, cases in which pneumonitis has been associated with quinidine treatment have not been reported previously in the literature.

**CASE REPORT**

A 54-year-old mason, a former smoker, was admitted to our hospital on July 1, 1992, for the evaluation of a 10-day history of fever and rapidly progressing lung infiltrates. He had been incapable of work for the previous year because of an accidental fracture of a lumbar vertebra. During the preceding 2 months he had been admitted to a district hospital 3 times because of episodes of atrial fibrillation, which were treated with digoxin or quinidine sulfate. This treatment had been continued since June 18, 1992, with digoxin, 0.25 mg once a day, and quinidine, 400 mg twice a day. Four days after the latter date he developed a fever of 38 to 39° C and felt ill, and on the seventh day, the first chest radiograph was taken, which revealed delicate nodular infiltrates.

Ceftizoxime treatment was initiated by a general practitioner, but the fever continued, and a dry cough and dyspnea developed; he was admitted to the district hospital 12 days after the beginning of quinidine and digoxin therapy.

The lung infiltrates progressed during the next 2 days and he was sent to our hospital. At the time of hospital admission, his general condition was good; his temperature was 37.9° C, but he was not dyspneic at rest. Neither rash nor adenopathy was found, but inspiratory rales were heard in both basal lung fields. His heart beat was regular.

Laboratory findings included the following values: an erythrocyte sedimentation rate of 95 mm in the first hour; C-reactive protein of 134 mg/L (<10 mg/L); a peripheral white blood cell count of 8,300/mm³ with 3 percent eosinophils; serum creatinine of 101 µmol/L (60 to 115 µmol/L); and a serum level of angiotensin-converting enzyme of 113 U/L (34 to 160 U/L). Antinuclear antibodies were negative. Arterial blood gases were not determined at the time of hospital admission.

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A chest radiograph (Fig 1) revealed small nodular infiltrates diffusely in both lungs and some pleural plaques, but the cardiac volume was normal and there were no signs of cardiac failure. A high-resolution computed tomographic scan of the chest showed bilateral parenchymal nodules (Fig 2). The PPD with 2 TU at 72 h was negative and sputum smears showed no acid-fast bacilli. No evidence of bacterial or viral infection was found.

Lung function tests showed mild restriction, with a vital capacity of 3.65 L (66 percent of predicted) and a forced expiratory volume in 1 s of 2.71 L (61 percent of that predicted). Diffusing capacity (Dco) was 6.47 mmol/L/min/kPa (69 percent of that predicted) and Dco per liter alveolar volume was 1.28 mmol/min/kPa (84 percent of that predicted).

The patient was taking no other drugs except for quinidine and digoxin, and he had not been exposed to any organic dust. A reaction to quinidine therefore seemed most likely, and the drug therapy was stopped at the time of hospital admission. Two days later, he was afebrile.

Bronchoalveolar lavage (BAL) on the sixth day after hospital admission showed an increased total cell count, 316X10⁶/L lavage fluid (127±65X10⁶), containing 82 percent macrophages, 17 percent lymphocytes, and 1 percent eosinophils. A number of macrophages showed cytoplasmatic vacuolization and the lymphocytes folding the nuclear membrane with an enlarged cytoplasm, interpreted as signs of activation. The IgG content of the lavage fluid was also elevated 10-fold relative to reference values.

Transbronchial biopsy specimens of the right lower lobe revealed patchy areas of mild interstitial fibrosis and inflammatory cell infiltrates, mainly plasma cells and lymphocytes (Fig 3). Some areas also showed an increased number of type 2 pneumocytes suggestive of alveolar wall injury. A few asbestos bodies were seen. The dyspnea and cough gradually diminished and the patient's condition improved. He was discharged from hospital on the eighth day with digoxin medication. A chest radiograph showed some clearing.

One month later the patient was admitted to the hospital for rechallenge with quinidine. He was well and his chest radiograph was normal except for the pleural plaques (Fig 4, left). His lung function test results were almost normal, with a vital capacity of 4.2 L (80 percent of that predicted) and an FEV₁ of 3.13 L (71 percent of that predicted). The Dco was normal, 9.19 mmol/L/min/kPa (90 percent of that predicted). He was given 100 mg of quinidine sulfate three times at intervals of 4 h, and 2 h after the third dose, he had chills and a fever (38.3°C). On the next day,
his chest radiograph showed diffuse small nodular infiltrates in both lungs (Fig 4, right).

He was discharged from the hospital on the third day afebrile and in good condition. A chest radiograph at 2 months once again was normal (except for the pleural plaques).

**Discussion**

The list of agents implicated in drug-induced pulmonary disease is expanding rapidly, but quinidine has not been included in the list. To our knowledge, this is the first reported case of quinidine-induced pneumonitis to be confirmed by means of a rechallenge with quinidine. It seemed from the beginning that there was no need for a large selection of differential diagnostic possibilities. Our patient's history, with a rapid onset of fever following the beginning of daily quinidine therapy, was most consistent with a hypersensitivity drug reaction. Quinidine fever typically occurs between 3 and 9 days of the onset of therapy, as in our case, and usually disappears within 14 to 48 h of the cessation of therapy. Our patient's pneumonitis fulfills the criteria for hypersensitivity pneumonitis: acute onset of symptoms (dyspnea, cough, fever) unrelated to the cumulative dose of the drug or the duration of the therapy, typical radiographic manifestations (peripheral acinar infiltrates or diffuse reticular infiltrates), elevated erythrocyte sedimentation rate, peripheral blood eosinophilia, lymphocytosis in the BAL fluid, and a favorable prognosis after discontinuation of the drug therapy alone. Our patient had normal peripheral blood eosinophils, but blood eosinophilia occurs only in some patients with hypersensitivity pneumonitis, and the proportion of lymphocytes in the BAL fluid (obtained 6 days after the cessation of quinidine therapy) was in the normal range, although the absolute number of lymphocytes was elevated. We therefore think that the pneumonitis was a hypersensitivity reaction to quinidine.

Analyses of BAL fluid cell findings in cases of drug-induced lung disease, especially that induced by amiodarone, have variously included lymphocytosis, neutrophilia, eosinophilia, or normal differential cell counts, and a recent report suggests that such analyses are not reliable in distinguishing between patients with amiodarone-induced pneumonitis, amiodarone-treated patients with other lung disease, and patients with interstitial lung disease. The different cell counts found in cases of amiodarone-induced pneumonitis may result from the mechanisms of pneumonitis, which are not known. Both direct toxicity of the drug and hypersensitivity injury have been speculated.

The use of quinidine for the treatment of cardiac arrhythmias is decreasing, partially because of cardiovascular or other toxicity and partially because of the availability of new, better drugs. If it is used, however, and the patient develops a fever or symptoms involving the respiratory tract, the possibility of quinidine side effects should be remembered. In this way, the needless use of often toxic and expensive antibiotics and the occurrence of irreversible fibrotic pulmonary changes would be avoided.

**References**

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**Noncardiogenic Pulmonary Edema Induced by Sublingual Buprenorphine**

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A 21-year-old woman developed noncardiogenic pulmonary edema within 90 min after the use of buprenorphine, 0.2 mg, sublingually for severe dysmenorrhea. No organic cardiovascular illness was detected. The pulmonary edema resolved spontaneously with conservative treatment. The mechanism of pulmonary edema may be an allergic reaction to buprenorphine. (Chest 1994; 106: 306-08)

Buprenorphine is a synthetic opioid with mixed agonist-antagonist properties with a potency 40 to 50 times that of morphine. It has a slow onset, but duration of action extends to 7 to 8 h. It is very effective in relieving moderate to severe pain when administered sublingually. Buprenorphine has been widely used to treat pain associated with cancer and also postoperative pain.

The recognized side effects are no greater than those of morphine; they are nausea, vomiting, and minimal effect on the cardiovascular and respiratory symptoms. There are some reports that sublingual buprenorphine caused near-fatal auditory hallucination and prolonged respiratory depression. Buprenorphine has a high therapeutic ratio, postulated as being due to the agonist-antagonist nature. We report a case of acute pulmonary edema associated with buprenorphine. To our knowledge, this has not been described previously.

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