of the aforementioned behavioral side-effects which was relieved only by discontinuance of the drug. Although the patient was hypotensive, which may have contributed to the extreme hypersonomolence observed upon admission, there was no evidence of other causes of hypersonomolence such as narcolepsy, sleep apnea, depression, congestive heart failure, Kleine-Levin syndrome (hypersonomolence associated with hyperphagia), hypoventilation syndrome, intracranial tumor or any metabolic or toxic condition. The diagnosis of beta-agonist-induced hypersonomolence is supported by the history of the onset of symptoms soon after the intake of the drug, by the lack of an identifiable cause for the clinical state other than the drug, and particularly, by the dramatic improvement following the discontinuation and recurrence upon readministration of the drug without the presence of hypotension.

The patient under discussion experienced hypersonomolence and somnolence with moderate doses of propranolol and atenolol, respectively, and sleepiness with subtherapeutic doses of both. The relative degree with which the beta-blockers might produce hypersonomolence would depend on the various properties of the individual drug such as lipophilicity vs hydrophilicity, receptor affinity, ratio of antagonistic vs agonistic activity, degree of membrane-stabilization, intrinsic sympathetic activity, serotonin blocking properties, and the dose administered. It has been shown that concentration of lipophilic beta-agonists in the brain is more than ten times that of plasma and is more likely to cause sleep abnormalities as opposed to hydrophilic beta-agonists. Discontinuation of prazosin probably had no effect on sleep because he had been taking it for several months before starting the beta-blockers without any change in sleep pattern.

There appeared to be an inverse relationship between the mean arterial blood pressure and the severity of somnolence. Johansson et al have reported impairment in the autoregulation of cerebral blood flow and damage to the blood-brain barrier of chronic hypertensive patients. This raises the possibility of periods of lowered cerebral perfusion exacerbating somnolence.

Gengo et al have reported that the CNS side-effects of beta-blockers were not dependent on their dose or relative lipid solubility. They have observed that both lipophilic and hydrophilic beta-agonists produce more or less the same degree of sedation. They attribute this effect to the concentration of drug at the receptor site concerned with the mediation of CNS effect, as well as the affinity and the number of receptors. Greenblatt et al have reported serious adverse reactions with subtherapeutic doses of beta-adrenergic blockers in elderly patients with impaired liver and renal functions. They attributed this effect to the intolerance of certain patients to the usual decrease in myocardial sympathetic stimulation.

Regardless of the mechanism, the clinical implication of this report is that both hydrophilic and lipophilic beta-adrenergic blocking agents can cause somnolence and hypersonomolence, particularly in the elderly and demented patients who may also have renal or liver dysfunction.

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Fiberoptic Bronchial Blockade in a Small Bronchopleural Fistula*

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A patient with bronchopleural fistula was successfully treated by selective intrabronchial injection of doxycycline and blood under fiberoptic bronchoscopic guidance. This simple and relatively noninvasive therapeutic approach is an effective and safe alternative in treating selective patients with a bronchopleural fistula.

Management of a pneumothorax is not a difficult problem as it usually responds to insertion of a thoracostomy tube and underwater-sealed drainage. Nevertheless, bronchopleural fistulae do occur in some patients and can lead to prolonged air leak. Under such circumstance, surgical intervention is indicated. When the patients present with poor respiratory reserve, however, the operation may have a higher risk.

We report a patient in whom successful treatment of persistent bronchopleural fistula was achieved by selective endobronchial injection of doxycycline and blood under bronchoscopic guide.

CASE REPORT

A 50-year-old man was admitted to the chest service of the Chang Gung Memorial Hospital on Aug 27, 1985, because of dyspnea. He has had complicated coal-miner pneumoconiosis for many years and was admitted to the hospital one month before this admission due to exacerbation of dyspnea. This time, he came with right chest pain

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Fiberoptic Bronchial Blockade (Lan et al)
and worsening of dyspnea. A chest roentgenogram revealed a 40 percent right pneumothorax and bilateral lung lesions that were consistent with a diagnosis of complicated coal-miner pneumoconiosis with bullous formation. Insertion of a chest tube along with underwater-sealed drainage was performed. In the following three months, the bronchopleural air leak persisted despite attempts at conventional management. Though surgical intervention seemed indicated in this patient, it was not performed because of poor respiratory reserve. After obtaining informed written consent, it was decided to plug the bronchopleural fistula from within.

On November 29, after overnight fasting and a local spray of 2 percent xylocaine, a flexible bronchoscope (Olympus BF P10) was introduced via nasal route. In order to suppress the cough reflex, 2 percent xylocaine was repetitively instilled into the bronchi as the scope was advanced. Then, a 5 F Critikon balloon wedge pressure catheter (a double-lumen catheter, with one lumen opens to the catheter-tip and the other to the near-tip inflatable balloon) was inserted through the suction-channel of the scope to each segmental bronchus of the right lung. With inflation or deflation of the balloon, each segmental bronchus could be occluded or opened selectively. When the lateral segmental bronchus of the right middle lobe was occluded, air leakage was no longer observed in the chest tube, and it recurred when the balloon was deflated. The catheter was then placed within this bronchus, and the balloon was inflated. Ten milliliters of the patient's own blood was injected into the bronchus through the lumen of the catheter. After a waiting period of five minutes to allow the blood to clot, the balloon was deflated, and the catheter was withdrawn along with the scope. After the procedure, the patient felt very much improved. One day later, however, he coughed up some bloody sputum and the shortness of breath recurred. Air leakage from the bronchopleural fistula was again noted. Two days later, the whole procedure was repeated. This time, 35 ml of patient's own blood was used for the intrabronchial injection. Similarly, the air leakage from the chest tube ceased, and the dyspnea improved immediately after the procedure. However, it lasted for one day only again. On December 6, the procedure was repeated once more. This time, 1 ml of doxycycline (20 mg) was injected into the lateral segmental bronchus of the right lung prior to the injection of 15 ml blood. The bronchopleural air leak stopped immediately and has not recurred since. The chest tube was removed ten days later on December 16. A pulmonary function test was performed on December 18 and showed a forced vital capacity of 1.16 L and a forced expiratory volume in one second of 0.78 L.

The patient was discharged on December 19 with long-term bronchodilator therapy. In the subsequent ten months, he was hospitalized three times with exacerbation of shortness of breath possibly due to viral infection. Otherwise, his condition has been stable.

**DISCUSSION**

Spontaneous pneumothorax usually responds well to insertion of a thoracostomy tube along with underwater-sealed drainage with or without suction. Surgical treatment is required only when the thoracostomy tube drainage and suction is unsuccessful and when a bronchopleural fistula has formed. In the present case, a surgical intervention was untenable because of poor pulmonary reserve.

In 1977, Hartmann and Rausch performed successful fiberoptic bronchoscopic guided endobronchial blockage using tissue glue to stop the air leak in a 44-year-old man with pulmonary fibrosis complicating ankylosing spondylitis, who developed bronchopleural fistula four days after surgical removal of pulmonary aspergilloma and thoraco-plasty. The procedure was somewhat difficult because the tissue glue (methyl-2-cyanoacrylate) they used for plugging the bronchus solidified rapidly, in about ten seconds. In the same year, Ratliff et al. used a fiberoptic bronchoscopy to introduce a split shot to embolize the bronchus that fed a bronchopleural fistula in a 38-year-old man who received an open lung biopsy for adult respiratory distress syndrome. The procedure was successful, but the patient died of underlying progressive pulmonary fibrosis and respiratory failure a few days later. They also found, in an animal model, that the injectable blood clots, gelatin, gelatin-capsule-shaped silicon rubber plugs, machined brass screws, or sponge material are not suitable for embolization of the bronchus. In 1982, Keller et al. used a bronchoscopic injection of a liquid bioadhesive (isobutyl 2-cyanoacrylate) to occlude a bronchopleural fistula in a 72-year-old man who had a complicated open lung biopsy for end-stage pulmonary fibrosis. The early result in this patient was satisfactory. Unfortunately, the patient died ten days later due to recurrent pneumothorax on the same side.

In 1983, Roksvaag et al. used a similar technique to inject tissue glue (N-butyl-2-cyanoacrylate, Histoacryl) into the bronchus and stopped the air leak in two patients with bronchopleural fistulae that developed after pneumonectomy for bronchogenic carcinoma. In 1983, Pace et al. reported another animal model of endobronchial occlusion of bronchopleural fistulae with a special-designed detachable balloon. In 1984, Høšer-Madsen et al. reviewed their experiences in the management of bronchopleural fistula following pneumonectomy for bronchogenic carcinoma and concluded that healing of the fistula seems to be achievable in most cases treated by bronchoscopic application of silver nitrate to the fistulous opening at the bronchial stump.

In our case, we have demonstrated that intrabronchial injection of blood alone provided an immediate but temporary effect on stopping the air-leak from the fistula. Combination of injection of doxycycline and blood provided a persistent effect. Since doxycycline is an irritant drug, it could induce bronchial inflammation. As a result of inflammation, the bronchial mucosa may swell and the bronchial secretion and the mucus plugs may accumulate, providing a delayed but more long-lasting effect on stopping the air-leak from the fistula, thus helping the healing of the fistula. Thus, an endobronchial injection of doxycycline followed by injection of blood could provide a rational way to occlude the feeding bronchus of the fistula. In addition, the blood clot in the proximal bronchus could prevent the spread of the injected doxycycline to other bronchoalveolar tissue, and therefore, may limit the possible chemical lung injuries to a very small area of the lung.

**CONCLUSION**

We conclude that selective endobronchial injection of doxycycline followed by injection of blood could be a potential solution in treating selective patients with bronchopleural fistula.

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Pulmonary Involvement in Zinc Fume Fever

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A patient with the clinical history of recurring zinc fume fever underwent an experimental welding exposure; this resulted in a systemic reaction and a distinct self-limiting response in the periphery of the lung, demonstrated by pulmonary function tests and bronchoalveolar lavage. These pulmonary changes observed for the first time in man were reproducible.

Metal fume fever has been known for over a century as an occupational disease that is induced by intense inhalation of fresh metal fumes with a particle size smaller than 0.5 μ. The fumes originate from heating the metals beyond their boiling point, as happens, for example, in welding operations. Oxidation usually accompanies this process. In most cases, this syndrome is due to exposure to zinc oxide fumes; however, other metals like copper, magnesium, cadmium, manganese, and antimony are also reported to produce such reactions.1,2 The starting point of our investigations was a patient with the history of a recurring zinc fume fever. In this patient, we used pulmonary function tests and bronchoalveolar lavage to examine the changes in the pulmonary tissue following the inhalation of zinc oxide fumes generated in welding processes.

CASE REPORT

Up until 1980, the now 26-year-old locksmith, a smoker (25 cigarettes per day), was well. In that year, he started a new job with much welding, usually without safety precautions such as a protective mask and adequate ventilation. A few hours after welding on zinc-coated materials for the first time, the patient developed shivering, sweating, and shortness of breath. Whatever welding technique he used, these complaints recurred many times when he was working with zinc materials. Other metals did not produce any symptoms. The discomfort always ceased spontaneously until the following day.

Clinical Findings

When referred to us, the patient was asymptomatic and had normal findings on physical examination, electrocardiogram, chest x-ray film, and all routine laboratory tests. Pulmonary function (equipment and methods, see König et al3) including inspiratory vital capacity (IVC), total lung capacity (TLC), airway resistance (Raw), forced expiratory volume in one second (FEV1), transfer factor (single-breath method, Dsb), and blood gas levels at rest as well as during exercise gave normal results.3 Merely the inhalation challenge with methacholine revealed a low-grade nonspecific bronchial hyperreactivity (five breaths of a 3 percent nebulized methacholine solution increased the Raw from 0.22 to 0.57 kPa×s×L⁻¹; a positive reaction is presumed in our laboratory when the Raw exceeds 0.35 kPa×s×L⁻¹ and the increase is greater than 0.2 kPa×s×L⁻¹).

Challenge Tests

With an interval of six months, we made two exposure tests under working conditions and laboratory control; the patient welded one hour on a zinc-coated tube with an electric torch. The fume was sampled in part by a constant flow sampler (Dupont model S 2300) for analysis. Blood levels of zinc and cadmium were measured after both tests (methods according to Stoeppler et al4 and Vieira and Hansen5).

RESULTS

The Raw was slightly increased immediately after the welding process (Fig 1), but in one hour, it was in the normal range again without any treatment. Two hours after the end of the challenge, the patient experienced a sweetish taste, shortness of breath, and a chilling sensation; one hour later, there were pronounced chills, and three hours later, the patient showed profuse sweating.

With a maximum three to six hours after the end of the exposure, we found a significant reduction of the IVC (from 5.25 L to 3.1 L), Dsb (40 percent of initial value), and the arterial oxygen partial pressure (PaO₂, 9 mm Hg), while the body temperature was raised to 38.5°C and the peripheral blood leukocyte count to 24 g/L (Fig 1). The subsequent chest x-ray film and the findings from physical examination of the lungs were normal. On the day after the welding test, the patient was nearly asymptomatic, and the pulmonary function test results were without abnormal findings, except for a slightly decreased Dsb (77 percent of the predicted value). A second trial, which was done after a six-month symptom-free interval with no contact to zinc fume welding on zinc-coated tubes, elicited a systemic and a pulmonary reaction of the same kind and degree as the first test.

The analysis of the sampled dust showed a high portion of zinc (2.0 mg of a total quantity of 6.12 mg), whereas only a small amount of cadmium, which often occurs as a contaminant in zinc and is feared because of its toxicity,6 could be found (0.02 μ). In accordance with that, the blood level of zinc was significantly increased after both tests, but the cadmium concentration was normal (Table 1). We performed two bronchoalveolar lavages as described previously.7 The first bronchoalveolar lavage was done one day after the second challenge test, when the patient was free of symptoms again and the pulmonary function tests all gave normal results. The total cell count of the lavage material was ten times as high as normal (total cell count, 94×10⁶), and the differential cell count showed a marked increase of polymorphonuclear leukocytes. Another bronchoalveolar lavage was performed after a period of seven weeks without any contact to zinc fumes. The total cell count (7.3×10⁶) and the differential cell

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