Alveolar Damage due to Inhalation of Amitrole-Containing Herbicide*

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Amitrole-containing herbicides are commonly used by home and cottage owners for spraying grass. They are manufactured and distributed in the United States, Canada and throughout the world by several pharmaceutical/chemical industries under many different trade names, such as Amitrole-T, Amizol, Azolan, Cytrol and Weedazol. They have not been previously associated with pulmonary toxicity in man or laboratory animals. We describe the first case in which inhalation of amitrole herbicide resulted in diffuse, asymmetric, severe alveolar damage, which was reversed after treatment with high-dose corticosteroids.

(Chest 1992; 101:1174-75)

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\text{pH} = \text{negative logarithm of hydrogen ion activity; } PCO_2 = \text{partial pressure of carbon dioxide; } PO_2 = \text{partial pressure of oxygen}
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Amitrole-containing herbicides are commonly used by homeowners on their lawns. Their toxicity is thought to be limited to mucosal membranes (skin, eyes), resulting usually from the direct contact with the herbicide. No specific respiratory precautions regarding wearing of protective masks are recommended by the manufacturers of this herbicide. This simply reflects a commonly held belief that because of low dose, low acute toxicity and large size of sprayed droplets, the risk of adverse pulmonary side-effects is negligible. In this report we describe a case of direct pulmonary damage resulting from the inhalation of amitrole-containing herbicide.

CASE REPORT

A 74-year-old previously healthy ex-smoker was spraying amitrole-containing herbicide (Go-up Backyard Clean-Up, Rhone-Poulenc) in his yard. He was referred to St. Michael's Hospital (Toronto, Ontario, Canada) for evaluation of mild dyspnea on exertion and chronic cough of 3 weeks duration. He was a chain-smoker for 50 years and had been exposed to cigarette smoke for 40 years with occasional second-hand smoke from his wife. He had also worked for many years in a public stadium and was exposed to smoke from special lamps used for halogenating the atmosphere. He denied exposure to other airborne toxins or organic dust.

He was stable and was afebrile on admission. Physical examination showed rales in both lower lung fields. Arterial blood gases were within normal limits. Chest radiographs revealed a diffuse bilateral pleural effusion that was noted to be increasing. The patient also had a prolonged wet cough and nonproductive sputum. He was treated with high-dose corticosteroids and his symptoms improved. He was discharged home and his cough and dyspnea significantly improved.

No precipitating antibodies to such common hypersensitivity antigens as Aspergillus, thermophilic Actinomyces, and Micropolyspora faeni. Viral, Mycosplasma and Legionella serological studies were negative.

A radiograph of the chest (Fig 1, center) showed an extensive infiltrate involving almost the entire left lung; a much less extensive patchy infiltrate also was noted on the right side. Computed tomography of the chest confirmed the presence of the infiltrate and in addition demonstrated bilateral pleural effusions, which were larger on the left side. Pulmonary function tests showed lung restriction with a total lung capacity measured in a body plethysmograph of 4.7 L (73 percent of predicted value) and vital capacity of 1.6 L (43 percent). Single-breath diffusing capacity for carbon monoxide was reduced to 10.7 ml/min/mm Hg (57 percent of predicted value).

Fiberoptic bronchoscopy showed airway erythema but otherwise no abnormalities. Bronchial brushings and washings revealed no bacterial (including Mycobacterium tuberculosis) or fungal growth. Transbronchial lung biopsy demonstrated a fibrinous and neutro-

FIGURE 1. Posteroanterior radiograph of the chest four days prior to exposure (left), three days after exposure (center) and 13 days after exposure (right).
Figure 2. Detail of transbronchial lung biopsy specimen. Diffuse alveolar damage with early organization is seen. There is a persisting fibrinous exudate (small asterisks) with hyaline membrane (small arrows); widening of alveolar septa with interstitial fibroblast proliferation (large asterisk) and prominent type 2 pneumocytes (large arrows) (Hemalum, phloxine, and saffron, original magnification ×250).

philic exudate in the alveolar spaces with hyaline membrane formation (Fig 2). There was early organization with proliferation of fibroblasts and type 2 pneumocytes with widening of alveolar septa. Special stains for fungi and Pneumocystis were negative. No viral inclusions were detected. These findings are consistent with diffuse alveolar damage of several days duration, which is more in keeping with a toxic rather than allergic alveolitis.

The patient was treated with high-dose intravenously administered corticosteroids. There was marked symptomatic and radiographic improvement within 48 h. A follow-up chest radiograph (Fig 1, right) obtained 10 days after admission showed almost complete resolution of the previously noted abnormalities. Pulmonary function tests obtained on the same day showed an increase in total lung capacity to 6.6 L (104 percent) and an increase in vital capacity to 3.3 L (88 percent); the diffusing capacity, although improved, still remained reduced at 15.6 ml/min/mm Hg (69 percent).

The patient brought the unused portion of the compound to the hospital. Microbiological examination was negative and the composition of the compound was confirmed with the manufacturer.

Discussion

Co-op Backyard Clean-up, also known by its product name Amitrole-T, is a commonly used herbicide containing 19 percent of aminotriazole, which is the active ingredient; 17 percent ammonium thiocyanate, which enhances the herbicidal activity of aminotriazole; less than 1 percent of sodium dioctylsulfosuccinate; and less than 1 percent of ethylene oxide. The product is an aqueous solution of these chemicals and is packaged as a 500-ml solution containing 100 g of amitrole.

The active ingredient, amitrole, is a water-soluble compound whose chemical formula is C₉H₈N₂, and proper chemical name is 3-amino-1,2,4-triazole; it also is referred to by the name aminotriazole. It was first introduced into commercial use in 1954 and is a common constituent of commercial herbicides. Its mechanism of herbicidal action is due to inhibition of chlorophyll formation and regrowth from buds.

There is little information in the scientific literature of any toxic effects of this compound. It has a weak carcinogenic potential in laboratory animals (causing thyroid and liver tumors in rats and mice), but not in man. Direct human toxicity appears to be limited to cutaneous allergies, and one case of allergic contact dermatitis occurring in a weed control operator has been described. There have been no previous reports of pulmonary toxicity to this agent.

The herbicidal preparation used by our patient contained, in addition to amitrole, ammonium thiocyanate—a salt which enhances the herbicidal activity of aminotriazole. Thiocyanate is a metabolite of cyanide and is cleared rapidly from the body without much being absorbed. Direct alveolar injury in response to thiocyanate has not been described. Acute effects of a massive respiratory dose of cyanide include collapse and respiratory arrest. Chronic effects of exposure to thiocyanate include nervousness, dizziness, nausea and vomiting. Although inhalation of ammonium thiocyanate has not been associated with alveolar damage, it is possible that in combination with aminotriazole it may have been responsible for the severe lung injury observed in this patient.

In view of the remarkable lack of previous reports describing pulmonary toxicity of this herbicide, we were perplexed as to why such a case should arise now and we wondered if the herbicide caused the severe pulmonary disease seen in our patient. We believe that the evidence, although circumstantial, is quite strong. The patient had no prior lung diseases and had a normal chest x-ray film one week prior to exposure. There was a clear temporal relationship between the exposure to the agent and the onset of disease, there was nothing in the history and extensive laboratory investigations to suggest infection, and there was a prompt response to corticosteroid therapy without any concomitant antimicrobial therapy. We believe that the reason for the development of pulmonary disease is due to a large amount of the agent inhaled by this patient within a short period of time.

The radiologic appearance of the chest seen in this case is unusual for the inhalational lung diseases, which most commonly present as symmetric, bilateral, interstitial infiltrates. Pleural effusions are not usually seen. A dense, asymmetric, alveolar pattern with bilateral pleural effusions as seen in our case must be extremely uncommon. It can only be speculated that the asymmetry is probably due to the underlying bronchitis and emphysema, causing misdistribution of ventilation with preferential airflow to the left lung.

We postulate that the lung injury caused by this herbicide was secondary to either direct toxic damage to the alveolar lining cells or an allergic reaction in the lung. The latter possibility is less likely, since the pathologic findings were not those of a granulomatous interstitial pneumonia, this being the histologic hallmark of hypersensitivity pneumonia. The response to corticosteroids cannot be used to differentiate between the allergic or direct toxic injury, since both processes are expected to respond similarly.

In summary, this case illustrates that inhalation of a large amount of common commercial herbicide, previously thought to be free of pulmonary toxicity, may be associated with acute toxic reaction of the lung. A protective oronasal mask should be worn when using this herbicide. When faced with a patient presenting with acute respiratory illness...
acquired during a short stay in a rural area, such as a farm or cottage, it is prudent to enquire about exposure to herbicides.

ACKNOWLEDGEMENT: We wish to thank Ms. C. Lukinuk of the Drug Information Centre at St. Michael's Hospital for the very extensive literature search to accumulate the known toxic effects of amitrole and thiocyanate.

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Pneumomediastinum Causing Pneumoperitoneum*

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Pneumomediastinum is characterized by the presence of air in the mediastinum and has been recognized since 1827, when described by Laennec. To the best of our knowledge, pneumoperitoneum as a result of spontaneous pneumomediastinum has not yet been described in the English literature. We observed and treated a young patient in the intensive care unit who presented with spontaneous pneumomediastinum. Free intra-abdominal gas was observed on the chest x-ray film on the day after admission. Management was conservative. Intra-abdominal and mediastinal air disappeared within four days. This condition, when recognized, needs only observation; we report this as a medical curiosity. (Chest 1992; 101:1176)

Free intra-abdominal gas is usually present on roentgenographic examination when perforation of a hollow viscus occurs or after a recent laparotomy. We found intra-abdominal air on the chest roentgenogram of a patient who presented with spontaneous pneumomediastinum and subcutaneous emphysema. This condition does not require special medical attention when other intra-abdominal pathologic findings have been ruled out.

CASE REPORT

A 20-year-old soldier was admitted to the hospital with a severe attack of bronchial asthma. The clinical picture consisted of respiratory failure, and the patient required endotracheal intubation.

On the control chest roentgenogram, pneumomediastinum had been noticed. Extensive subcutaneous emphysema of the neck and chest wall developed, and bilateral chest tubes were inserted. On the following day a chest x-ray film revealed free intra-abdominal gas (Fig 1), but clinically, the findings from abdominal examination were unremarkable. Two days later, the patient was extubated; pneumoperitoneum and pneumomediastinum resolved within four days.

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FIGURE 1. Chest roentgenogram showing presence of free air under right and left hemidiaphragm. Note prominent subcutaneous emphysema and pneumopericardium.

DISCUSSION

Spontaneous pneumomediastinum is a rare, but well recognized pathologic condition.1,2 The pathogenesis seems to be related to a sudden elevation in pulmonary pressure as a result of chest trauma, excessive cough, assisted ventilation, or the Valsalva maneuver.

Chest roentgenographic signs that permit the diagnosis of pneumomediastinum include pneumopericardium, pneumothorax, and "thymic sail sign." Different roentgenologic patterns that depend on the routes of free air dissection, such as subcutaneous emphysema, periaortic air, pneumoretroperitoneum and the collection of the gas between the parietal pleura and the diaphragm, can be observed.

It is a well-established fact that a number of areas of the diaphragm may give way under pressure from the abdominal viscera. Most diaphragmatic hernias start in the small areas of weakness, such as posterolateral (Bochdalek) or parasternal (Morgagni) defects, and enlarge with age.

The defect may be as small as 1 cm in diameter, and a sac (parietal peritoneum) is absent in 85 percent of the cases in this pathologic condition.3 In such circumstances, communication between the mediastinum and the abdominal cavity may exist. The presence of this condition in our patient can explain the migration of air from the mediastinum to the abdominal cavity as a result of a sudden increase of the intramediastinal pressure.

Pneumoperitoneum by this mechanism undoubtedly does not require special care and is described by us as an incidental finding and medical curiosity.

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