COMMENTARY  This commentary provides editorial perspectives on the report which follows

Vinyl Chloride and Polyvinyl Chloride Exposure and Occupational Lung Disease

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Several recent reports,1,2 and one in this issue (see page 825), have contributed new observations on pulmonary disease in vinyl chloride (VC) and polyvinyl chloride (PVC)-exposed patients.

Earlier reports, a few even preceding the identification in 1974 of vinyl chloride as a human carcinogen (with hemangiosarcoma of the liver the marker tumor, but most probably not the only tumor), had centered on the rather unexpected occurrence of roentgenographic abnormalities3-8 or pulmonary function impairment,3,7-10 or had indicated dyspnea as a prominent symptom6,11 in VC- and/or PVC-exposed workers.

The roentgenographic pattern described was essentially that of reticular-linear and/or nodular (small rounded) opacities, involving both lungs, predominantly in the lower zones. Pulmonary function abnormalities, both restrictive and obstructive dysfunction, have been observed, with diffusion defects and arterial desaturation in some cases.

Two recent reports, one a case report,1 the other an epidemiologic survey,2 seem to identify PVC dust as the etiologic agent in a peculiar type of pulmonary fibrosis associated with a granulomatous reaction. Electron microscopic examination showed the giant multinucleated cells to contain a nonhomogenous material in their cytoplasm, which was identified to be PVC. A similar pattern was reproduced by incubation of human macrophages obtained by bronchial lavage, with PVC powder: absorption of PVC particles in the cytoplasm was rapid, with thinly granular lysosomal material deposited against the PVC particles.

Similar histologic lesions had been previously described in a human case8 and in an experimental study in guinea pigs and rats.12

Exertional dyspnea, diffuse micronodular chest roentgenographic abnormalities, and restrictive pulmonary dysfunction were the main characteristics in the case of PVC pulmonary fibrosis associated with granulomatous lesions.1 Experimental intratracheal administration of PVC dust in rats13 has been shown to result in an increase in the activity of lysosomal enzymes, interstitial fibrosis, and granulomatous lesions surrounded by fibroblasts, reticulin, and collagen fibers.

An epidemiologic study of a large group of PVC- and VC-exposed workers12 detected 20 cases of "typical pneumoconiosis," i.e., chest roentgenogram changes consisting of irregular opacities or micronodular shadows of at least class 1 profusion, according to the ILO U/C classification. All these cases were found among PVC-exposed employees. The pattern of roentgenographic abnormalities described is very similar to that reported in the case in which the lung biopsy specimen revealed fibrosis and granulomatous reaction, with inclusion of PVC particles.

The same study reported the presence of less marked roentgenographic abnormalities, of the linear- reticular type, in a much larger proportion (32 percent) of the population examined; these changes were present in VC monomer-exposed and in PVC-exposed employees. While the prevalence was higher in smokers than nonsmokers, 65 of the 388 abnormal x-ray films were found in individuals who had never smoked. This observation is relevant since the pulmonary effects of vinyl chloride monomer per se are of great interest.

In the context of the multiorgan effects of vinyl chloride, including the peculiar syndrome of acroosteolysis, scleroderma-like skin changes, vascular changes affecting the arteries, arterioles, and capillaries of hands and fingers, liver and spleen capsular fibrosis, liver fibrosis, abnormalities of the sinusoidal vessels in the liver, and portal hypertension, Ward et al14 investigated the immunologic status of 58 workers from a VC polymerization plant. The findings included hyperimmunoglobulinemia, cryoglobulinemia, cryofibrinogenemia, in vivo complement activation via the classic pathway, with C4 and C3 conversion and an increase in the B cell lymphocyte population. Immunofluorescent examination of skin, muscle, and lung biopsy specimens revealed the presence of circulating immune complexes, with deposition on vascular endothelium and occlusion of small vessels. In areas with subintimal proliferation
and luminal occlusion, there was immunoglobulin, complement, and fibrinogen deposition in the sub-intimal regions of the vessel wall. The presumed sequence of changes was thought to be structural alteration of protein molecules, as a direct effect of a highly reactive metabolite of vinyl chloride, eliciting an immune response, with activation of B cells and hyperimmunoglobulinemia. Cryoprecipitable immune complexes (antigenic altered protein plus immunoglobulin) activate complement, with consequent vascular occlusion, through fibrinogen/fibrin conversion and polymerization. Collagen synthesis is stimulated in these ischemic areas.

Similar abnormalities of the immunologic status were found in another study of 22 workers exposed to vinyl chloride, with Raynaud’s syndrome, and in some cases, acroosteolysis. Latent cryoglobulinemia was detected in 18 cases, with increases of immunoglobulins, IgA and IgG.

Circulating cryoimmunoglobulins are a prominent feature of idiopathic pulmonary fibrosis and increased IgG levels have been shown to be characteristic for bronchoalveolar lavage fluid of such patients.

Interstitial pulmonary fibrosis is a possible effect of vinyl chloride exposure; the occurrence of more dramatic and specific abnormalities in other organ systems—liver, spleen, and peripheral circulation—has probably prevented more focused attention on pulmonary effects of vinyl chloride in the past.

Long-term effects of vinyl chloride include well-documented carcinogenicity. Lung cancer has been found to occur with an increased incidence in several mortality studies. In experiments on mice, Suzuki has described hyperplastic changes of the alveolar lining cells and pulmonary tumors in the majority of exposed animals. The ultrastructure was thought to indicate that the tumors originated in type 2 alveolar cells. Alveologenic tumors were also described in several other experimental studies. Interestingly, other known carcinogens, such as polycyclic aromatic hydrocarbons, nitrogen mustard, and chromates produce pulmonary tumors in experimental animals similarly, originating in the type 2 alveolar cell.

The effects of vinyl chloride-polyvinyl chloride exposure on the respiratory system of exposed workers seem to indicate two patterns of nonmalignant effects: a granulomatous reaction, to PVC dust, with inclusion of PVC particles in macrophages and histiocytes, and associated interstitial fibrosis, and an interstitial pulmonary fibrosis due to vinyl chloride monomer effect on protein molecules and the immunologic mechanisms triggered by the altered protein.

The long-term carcinogenic effect, with a significant increase in the incidence of lung cancer also is of concern, although the magnitude of this effect has not yet been completely evaluated.

REFERENCES


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VINYL CHLORIDE AND POLYVINYL CHLORIDE EXPOSURE
Pulmonary Manifestations of Vinyl and Polyvinyl Chloride (Interstitial Lung Disease)*

Newer Aspects


Newer varieties of occupational lung diseases primarily due to the vast increase in industrial technology have been reported recently. Preeminent among such newer agents are vinyl chloride (VC) and polyvinyl chloride. Very few cases have been reported, in Europe only, with descriptive histopathologic changes. To our knowledge, no pathologic studies of VC exposure have been described in the American literature. The biopsy abnormalities in our patients disclosed desquamation of alveolar macrophages into the alveolar lumina and minor interstitial and alveolar inflammatory changes. Pulmonary function abnormalities included restrictive insufficiency. Preventive therapy consists of the avoidance of further exposures, frequent industrial hygiene monitoring, and total avoidance of tobacco smoke, as well as associated atmospheric pollutants. Thus far, none of these patients has exhibited evidence of pulmonary neoplasm. All three patients survived their occupational injuries, and two are still disabled to varying degrees. Urine and blood levels of phthalic acid derivatives were elevated in two patients, the exact significance of which is not fully known. It probably represents a toxicologic response, but must be further pursued before conclusions can be reached.

N ewer varieties of occupational lung diseases have been reported recently, primarily due to profound advances in industrial technology. Preeminent among such newer agents are vinyl chloride (VC) and polyvinyl chloride (PVC), substances used extensively in the plastics industry. More than 18 billion lbs were produced in 1972, with approximately 25 percent produced in the United States. Between 36,000 and 50,000 workers were exposed at that time to VC or PVC fumes, either during the polymerization process or during the processing of finished products. The number of people exposed, owing to alteration of the finished product or destruction of these products, or simply to living near a plant where any of these diverse processes may take place, is unknown. However, evidence has been presented that such exposures may be harmful. According to a recent Environmental Protection Agency report, approximately 90 million kg of PVC are discharged annually into the atmosphere.

The emergence in 1974 of VC as a new occupational carcinogen, producing angiosarcoma of the liver, focused attention on other toxicologic manifestations of this group of chlorinated hydrocarbons. Pulmonary effects were first described in 1970, but few cases have been reported characterizing the histopathologic changes of the human respiratory tract, all published from abroad.

Three patients with extensive exposure to the fumes of either VC monomer or PVC are herein reported. Lung biopsy results and the implications of their exposures are discussed. In addition, ultra-microscopic findings are included, and new biochemical analyses are reported in two patients. A summary on this subject of PVC-induced disease was presented by the authors at a symposium in the Soviet Union in October, 1978.

MATERIALS AND METHODS

Our experience involves the diagnosis and management of three patients with a pathologic diagnosis of interstitial fibrosis and work-related exposure to either VC or PVC gas or solids. All three patients had a lung biopsy, one transbronchial, and one by open method.

Pulmonary function studies were done by the Systems Research Laboratory method and included total vital capacity, timed vital capacity, flow rate, and diffusion capacity with carbon monoxide. Arterial blood gas determinations were performed by the Instrumentation Laboratory method, and distribution studies were measured with the nitrogen washout method.

Routine screening tests included complete blood counts (CBC), urinalysis, serology, SMA-12 chemistry profile, ECGs, and sputum studies for routine bacteriology. Smears and cultures of sputum for fungi and Mycobacterium were also performed. Each patient also had a sputum cytologic examination. Immunologic testing was performed on each patient and is detailed under the case discussion.