Further information on aluminium inhalation in silicosis

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Abstract

Objectives—In previous studies, a significant reduction in biological activity of quartz by the surface chemistry of aluminium was noted. Aluminium lactate inhalation one month after quartz exposure significantly suppressed silicosis. In a recent study, it was noted that aluminium inhalation failed to alter the silicosis process after disease was recognised by standard chest radiography in the first year after monthly treatment.

Methods—That study was extended with the same groups of sheep, the aluminium treated group received weekly aerosol of 100 mg of aluminium lactate for an additional two years. All sheep were evaluated at three-month intervals by chest radiography, lung function, and lung lavage.

Results—The sheep with silicosis had significantly reduced lung functions, increased cellularity, phospholipids, and hyaluronan. These changes persisted for several years without significant differences between the silicotic sheep with or without the aluminium aerosol treatment.

Conclusion—Aluminium aerosol treatment of silicosis after radiographic recognition of disease and the end of exposure did not alter the disease process.

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The toxicity of quartz is largely related to its surface properties, and can be reduced by aluminium.1–2 Aluminium lactate in itself has no biological activity on lung tissue and its action is through binding to the surface of quartz so masking its chemical functions. The amounts of aluminium required to reduce disease in our earlier studies3–4 were well below the average amount of aluminium impurities in commercial table salt or in one tablet of gastric antacid. The reduction of the biological activities of quartz by aluminium and other surface active compounds has been documented in cell culture and in vivo, when the quartz was treated before exposure.3–4

In exploring further the activity of aluminium inhalation, we recently tested its power to alter the silicosis process one year after disease was recognised by standard chest radiography, which would be a realistic intervention time in the human condition. We found no significant effect of aluminium treatment at monthly intervals for one year. We therefore extended the study for another two years with treatments at weekly intervals.

Materials and methods

ANIMALS

Fourteen of the 24 sheep that were originally exposed to silica developed silicosis as determined by a definitely abnormal chest radiograph (category 1 or above in the International Labour Organisation (ILO) classification of radiographs).5 The 14 sheep exposed to silica had an abnormal chest radiograph of ILO category 1 or above after three years of 100 mg Minusil-5 in 100 ml saline intratracheal injections at 10 day intervals. Minusil-5 silica particles have been well characterised, 99-9% are of diameter < 5 μm and 95% < 1 μm. Exposures were carried out after nasotracheal intubation, with repeated slow infusions of the suspension in the trachea at 10 day intervals. The animals were studied before exposure and at three-month intervals by chest radiograph, pulmonary function tests, bronchoalveolar lavage (BAL) analyses, and necropsy histopathology in dead animals.

EXPERIMENTAL DESIGN

After month 36, the 10 control sheep were further exposed to intratracheal injections of phosphate buffered saline (PBS) at 10 day intervals. The 14 sheep with silicosis were divided randomly into two groups of seven. The silicotic sheep were exposed to PBS aerosol with or without the addition of 100 mg of aluminium lactate delivered through a Bird Mark 8 pressure ventilator (Bird Richmond, CA) as previously detailed,5–6 at monthly intervals for the first year and weekly for the following two years.

PROCEDURES

Chest radiograph

Each sheep was positioned on a mobile cart with a wooden board and a grid cassette under the chest. The x-ray filming technique was as previously reported with radiographs scored according to the ILO classification of radiographic profusion of parenchymal opacities6–7 with the extended 12 point scale. Readings of the films were done without other information, by one reader who had used the ILO system for over 15 years in humans and in sheep.

Pulmonary function tests

The methods used in the pulmonary function tests of the sheep have been published.5–7

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Composite figure of most pertinent and representative observations. *P < 0.05 v controls. There was no significant difference between the groups exposed to silica with or without aluminium aerosol treatments.

Bronchoalveolar lavage and fluid analyses
All techniques of BAL procedures and analyses have been previously described.24 In the BAL fluid supernatant, hyaluronan concentrations were measured by the technique described by Laurent and Tengblad.6 Other BAL variables used were cellularity and differential, total proteins, albumin, immunoglobulins, the enzyme lactate dehydrogenase, phospholipids, fibronectin, fibronectin production by macrophages in a 24 hour culture, fibroblast proliferation upon exposure to BAL fluids, and lung inflammatory cell hydrogen peroxide release.

Assessment of Progression of Disease
The following criteria were used to determine significant clinical progression of pneumoconiosis: an increase in the chest radiograph of two or more extended ILO categories of profusion of opacities on the extended 12 point scale; a deterioration in lung function of 10% or more of a functional variable; an increase of 100% or more of two or more BAL variables expressed per ml of BAL fluid.

Statistical Analysis
The data were evaluated by analysis of variance for experiments with repeated measurements on the same subjects. When a significant effect was detected, a Dunnett t test was used to find which group means were significantly different. To assess the significance of difference in individual changes in variables of disease activity, we used the $\chi^2$ test. For assessment of the effect on animal survival, we tested the equality of survival distributions for different groups with the Mantel-Cox and Breslow procedures. Differences with $P < 0.05$ were considered to be significant.

Results
The effects of three years of aluminium inhalation on the survival of the sheep were not significantly different in the groups, with parallel rates of mortality in the two silicotic groups; however, mortality was significantly higher in the silicotic sheep than in the controls ($P < 0.05$, figure).

The severity and progression of the disease was evaluated by chest radiograph and lung function tests. The control sheep had normal radiographs whereas those in the two silicotic groups had on the average an ILO concise category 2 disease, which did not change significantly over the three year period of study (figure). Similarly the altered lung function tests in the silicotic sheep were not significantly modified by aluminium treatment (figure).
The lung lavage previously reported in the silicotic sheep\(^7\) showed that the alveolitis with characteristics of cytotoxicity, lung matrix damage, and fibrogenicity had regressed substantially after the end of exposure, between months 36 and 48, but thereafter, remained significantly changed in activity above the controls in most variables. These lung lavage variables were also unaffected by three years of aluminium treatment (figure).

**Discussion**

This paper reports on the influence of three years of treatment with aluminium aerosol on silicosis radiographically detected in the sheep model. The disease was induced at a relatively low level of exposure as witnessed by the longer interval between exposures and by the longer exposure time needed to induce silicosis than in earlier studies in our laboratory.\(^2\)\(^-\)\(^7\)\(^-\)\(^10\)

The disease reproduced in the sheep had the fundamental characteristics of human simple nodular silicosis, as documented in earlier studies.\(^2\)\(^-\)\(^10\) The disease produced ILO concise category 2 radiographic opacities, restrictive lung function alterations, and modifications on lung lavage consistent with silica induced alveolitis. Treatment was started one year after exposure had ended. We found no significant improvement of the silicotic condition on any of the radiographic, functional, or lung lavage variables.

In earlier studies of aluminium treatment of silicosis,\(^2\)\(^-\)\(^10\)\(^ 11\) we had documented a significant inhibition of toxicity of silica, when the quartz was treated before exposure and when treatment was started early after exposure. In this study, treatment was started one year after initial radiographic recognition of silicosis, which would constitute a likely simulation of the human condition. The serial measures of radiographic score of disease, the pulmonary function tests, and the analyses of lung lavages were not significantly changed by the aluminium treatments. For the clinician, these data are disappointing as it had been hoped that aluminium treatment would be of therapeutic interest at least in the early stages of the disease. These results are clear and are further supported by clearance studies\(^12\) that documented the half life of quartz coated with aluminium lactate inhaled for five months, compared with that of native quartz. They support the conclusions of an earlier study in humans.\(^1\)

The absence of effect on the clearance of quartz and on the disease induced could be related to the chosen concentration and treatment intervals (all possibilities have not been tested) or more likely because aluminium lactate may not come into contact with the quartz particles, already covered by surfactant, phagocytosed by macrophages, and migrated into the interstitium.

In conclusion, treatment of silicosis with aluminium aerosol after radiographic recognition of disease did not alter the disease process.

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