Pulmonary damage after modest exposure to zinc chloride smoke

B. ZERAHN*, A. KOFOED-ENEVOLDSEN†, B. V. JENSEN*, J. MØLVIG†, N. EBBEHøj†, J. S. JOHANSEN§ AND I.-L. KANSTRUP*

*Department of Clinical Physiol. and Nuclear Medicine, Herlev Hospital, University of Copenhagen, †Department of Endocrinology, Herlev Hospital, University of Copenhagen and §Department of Occupational and Environmental Medicine, Bispebjerg Hospital, University of Copenhagen and Division of Rheumatology, University of Copenhagen, Hvidovre Hospital, Copenhagen, Denmark

Thirteen soldiers (11 men and two women) were exposed to zinc chloride smoke (ZCS) during a combat exercise. Even though their initial symptoms were modest, a prolonged follow up with lung function testing and blood samples was undertaken due to previous cases with fatal outcome after exposure to ZCS. Four weeks after exposure there were statistically significant declines from baseline values in lung diffusion capacity and total lung capacity of 16.2% and 4.3%, respectively. At the same time plasma levels of fibrinogen and zinc were significantly elevated, though mainly within the normal range. All variables showed a tendency towards normalization at follow up 8 weeks and 6 months after exposure. These findings indicate an unexpected quantifiable damage to lung parenchyma with a remarkable delay after modest exposure to zinc chloride smoke despite sparse initial symptoms.

Exposure to high concentrations of ZCS may induce adult respiratory distress syndrome (ARDS) after a symptom free period of up to 12 days from exposure. Even though none of the soldiers in the present study developed ARDS the assessment of lung diffusion capacity and acute phase reactants is proposed as a supplement when monitoring patients after exposure to ZCS.

Introduction

Zinc chloride smoke (ZCS) screens are used for both military and civilian screening purposes. The use of these smoke bombs in confined spaces has been widely abandoned due to several lethal incidents (1-3). However, the use of ZCS in open air is considered safe within certain limitations (4,5).

Immediate symptoms after exposure may be irritation of the eyes and the upper respiratory tract with lacrymation, metallic taste, coughing, hoarseness and soreness of the throat, which in mild cases last from a few hours to a few weeks (6,7). In more severe cases nausea vomiting, chest pain, and headache also occur (8,9). Clinical and paraclinical findings include cyanosis, pyrexia, leucocytosis (mostly polymorfonuclear leucocytes), reduced vital capacity (VC) and forced expiratory volume in 1 sec (FEV1) at the peak of symptoms with recovery during convalescence, increased zinc urinary excretion and various degrees of hypoxemia. Chest radiographs may show diffuse infiltration that in some cases persist in various degrees without clinical symptoms. In more severe cases emphysematous bullae and pneumothorax occur (10).

Exposure to high concentrations may induce adult respiratory distress syndrome (ARDS) after a symptom free period of up to 12 days from exposure (11,12). The outcome is frequently fatal, and in such cases autopsies have shown extensive interstitial and intra-alveolar space fibrosis and arterial and venous lumen reduction as well as obliteration and widespread occlusion of microvessels. However, the exact mechanism by which ARDS is triggered is unknown (13). In exceedingly high concentrations of ZCS death is caused within hours by oedema of the larynx and spasm of the glottis (14). In lesser but still very high concentrations severe haemorrhagic ulceration and exorision of the upper respiratory tract may lead to a fatal outcome (1).

At present, only casuistic reports have dealt with diffusion capacity after ZCS exposure (11,15,16). We describe a 6-month follow up of lung function variables and specific serum variables in 13 soldiers, who were exposed to modest concentrations of ZCS during a routine military exercise.
Material and methods

PATIENTS

Thirteen soldiers, (two women and 11 men) aged 19 to 26 (median age 20 years) were exposed to ZCS during a combat exercise. Eleven of the soldiers were never smokers while the remaining two were present smokers (4.25 and 6 pack-years, respectively). The soldiers were together with nine unexposed colleagues either defending or attacking a combat exercise building with a wide door and window openings. A total of two smoke canisters were ignited in the open air, but due to wind conditions the smoke drifted into the combat exercise building through the open windows and doors. Two of the soldiers inside the building were exposed for 5–10 min without airway protection. The remaining 11 soldiers were briefly exposed while running through the plume of smoke and/or upon entering the combat exercise building.

Primarily 12 of the soldiers were hospitalized on the day of exposure for observation due to soreness of the throat, coughing, chest pain and mild headache. None of the soldiers had severe respiratory symptoms when admitted, but four of them complained of dyspnoea during the combat exercise.

Upon admittance all soldiers were treated with inhalation of 1 mg budesonide and 200 mg intravenous hydrocortisone followed by 75 mg oral prednisolone after 12 h. Four soldiers were then treated with oral prednisolone 40 mg daily for 1 week and then gradual reduction in dose with 5 mg every third day. Three of the soldiers were treated because of the duration and concentration of smoke exposition and the fourth was treated because of persistent coughing and chest pain. This soldier had a laryngoscopy 5 days after exposure, showing signs of hypopharyngeal inflammation interpreted as chemical pharyngitis. One soldier was treated for 18 h with intravenous N-acetylcycteine (140 mg kg⁻¹ day⁻¹) until blood samples were obtained showing normal values for plasma zinc.

The thirteenth soldier was admitted to hospital the day after exposure due to mild initial symptoms. He was not treated with steroids but joined the follow-up programme.

METHODS

All soldiers had spirometry and lung diffusion capacity testing performed using a Pulmonary Function Testing System 1070 (Medical Graphics Corp. Minnesota, U.S.A.). One soldier however, had her first lung function test performed at another hospital in Copenhagen county. The results from the latter test have been used as her baseline values and have not been presented in the preliminary study

The following pulmonary variables were recorded at each session: Vital capacity (VC), forced expiratory volume in 1 sec (FEV₁), maximal expiratory flow when xx% of the FVC remains to be delivered (MEFxx), total lung capacity (TLC), lung diffusion capacity with adjustment for actual haemoglobin content (DLCOcorr) and diffusing capacity per alveolar volume (DL/VA) were recorded (18). TLC and DLCOcorp were determined with the single breath technique after inhalation of a gas mixture containing carbon monoxide and neon with the latter as an indicator of the dilution. The better of two results that differed no more than 3% was used as the final test result. Only experienced lung function technicians performed the tests. Lung diffusion capacity was adjusted for haemoglobin level according to Cotes et al. (19).

Blood samples were obtained from all soldiers on the second day and subsequently after 1, 2, 4, and 8 weeks. At day 0 blood samples were obtained from 10 of the soldiers and 29 weeks after exposure from 11 of the soldiers. From these blood samples plasma levels of zinc, fibrinogen and C-reactive protein were determined along with haemoglobin, blood sedimentation rate and differentiated while blood cell counts. Also serum levels of YKL-40 (human cartilage glycoprotein-39) and the aminoterminal propeptides of type I and type III collagen (PINP and PIINP) were determined on each blood sample. YKL-40 is an 18 glycosyl hydrolase that has been suggested to function in the degradation of extracellular matrix or tissue inflammation (20,21). Both PINP and PIINP are regarded as markers of formation of collagen type I and III respectively (22,23). However, blood samples were only sufficient for determination of YKL-40, PIINP and PINP at day 0 and day 1 for 10 of the soldiers and from day 2 for 12 of the soldiers. Serum levels of YKL-40 and PIINP were determined by radiu immunoassays (20,23) and PINP by enzyme linked immunosorbent assay (22).

Radiographs of the thorax and arterial blood gas analyses were also obtained from day 1 after exposure and during follow-up.

DATA ANALYSIS

Changes in lung function variables and blood analyses with time were tested using the Wilcoxon non-parametric test for paired data and the Friedmann non-parametric test for several related samples.

Results

Data regarding changes in lung function variables for the 13 exposed soldiers are listed in Table 1. All baseline values for lung function were within normal range when compared to a Danish reference population (24). Significant declines in DLCOcorr, TLC, and ΔVA/VA were found, with the lowest values observed 4 weeks after exposure. MEF25 was also lower 4 weeks after exposure compared to baseline values, but the Friedmann test only showed a trend towards significance. The development of changes in DLCOcorr, compared to initial values is illustrated in Fig. 1. A significant increase in VC was found 2 weeks after exposure. During follow-up we observed no significant drifts or jumps with time during routine calibration tests of the pulmonary test system. We were not able to demonstrate any correlation between the degree of exposure,
Table 1. Lung function variables after mild exposure to zinc chloride smoke

<table>
<thead>
<tr>
<th>Weeks after exposure</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>29</th>
<th>Friedman test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median (25-75%)</td>
<td>median (25-75%)</td>
<td>median (25-75%)</td>
<td>median (25-75%)</td>
<td>median (25-75%)</td>
<td>median (25-75%)</td>
<td>Chi-square</td>
</tr>
<tr>
<td>TLC(l)</td>
<td>7.0 (4.5-8.5)</td>
<td>7.1 (4.4-8.8)</td>
<td>7.3 (3.8-9.2)</td>
<td>6.7 (4.3-9.0)**</td>
<td>7.0 (4.4-9.0)</td>
<td>6.8 (4.8-8.6)*</td>
<td>21.4***</td>
</tr>
<tr>
<td>VC (l)</td>
<td>5.4 (3.5-6.4)</td>
<td>5.4 (3.4-6.7)</td>
<td>5.7 (3.5-6.7)**</td>
<td>5.5 (3.6-6.5)</td>
<td>5.5 (3.6-6.5)</td>
<td>5.6 (3.6-6.8)*</td>
<td>20.2***</td>
</tr>
<tr>
<td>RV (l)</td>
<td>1.6 (1.3-2.0)</td>
<td>1.7 (0.8-2.3)</td>
<td>2.0 (0.8-2.3)</td>
<td>1.6 (1.0-2.0)</td>
<td>1.9 (1.0-2.1)</td>
<td>1.8 (1.3-2.1)</td>
<td>10.4(*)</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>4.6 (2.9-5.3)</td>
<td>4.7 (3.0-5.6)</td>
<td>4.6 (3.0-6.1)</td>
<td>4.6 (2.9-6.0)</td>
<td>4.7 (2.8-6.0)</td>
<td>4.5 (3.1-6.1)</td>
<td>8.6</td>
</tr>
<tr>
<td>MEF₂⁵₅ (l/s)</td>
<td>8.6 (6.3-11.6)</td>
<td>8.2 (6.1-10.6)</td>
<td>8.0 (5.3-10.6)(*)</td>
<td>7.5 (5.7-9.5)**</td>
<td>8.3 (5.7-9.9)</td>
<td>8.2 (6.3-10.1)</td>
<td>9.5(*)</td>
</tr>
<tr>
<td>DLCOcor (mM/min/mmHg)</td>
<td>14.2 (8.5-17.3)</td>
<td>13.2 (8.3-15.5)*</td>
<td>12.8 (8.2-15.1)**</td>
<td>11.9 (7.3-13.7)**</td>
<td>12.7 (7.3-14.9)**</td>
<td>13.7 (7.6-14.3)*</td>
<td>28.6***</td>
</tr>
<tr>
<td>DL/Va (mM/min/mmHg/l)</td>
<td>2.4 (2.1-3.0)</td>
<td>2.3 (1.8-2.7)**</td>
<td>2.2 (1.7-2.5)**</td>
<td>2.1 (1.7-2.4)**</td>
<td>2.1 (1.6-2.5)**</td>
<td>2.2 (1.8-2.8)</td>
<td>26.6***</td>
</tr>
</tbody>
</table>

Significance levels are indicated by asterixes: (*)P < 0.05; **P < 0.02; ***P < 0.01. Results from tests at week 1 through 29 are compared to values at day one by a Wilcoxon matched pairs test. A Friedman test is applied to test the null hypothesis that there is no difference in lung function throughout the follow-up period. For abbreviations see text.
None of the soldiers had leucocytosis upon admittance. But the initial levels of both neutrophils and monocytes were significantly higher than 29 weeks after exposure (36% and 25% respectively, \( P < 0.01 \)). Only the four soldiers who received oral prednisolone had levels of neutrophils above normal range during follow-up.

Plasma levels of fibrinogen were significantly elevated during a period from 1-8 weeks after exposure compared to initial values and some peak values exceeded normal range (Fig. 1). Plasma levels of zinc were above initial values at 2-8 weeks after exposure (Fig. 1). Individual peak levels for plasma zinc were dispersed over a wide range of time from the second day to 8 weeks after exposure and remained within normal range. Five out of the 13 soldiers had slightly elevated plasma levels of CRP and eight out of 13 had a slight increase in blood sedimentation rate during the period from 2-8 weeks after exposure. We were not able to demonstrate a correlation between changes in lung function variables and changes in plasma levels of zinc or fibrinogen.

Plasma level of YKL-40 increased by median 1118% from day zero to day two (\( n = 10, P = 0.005 \)). No differences from baseline values were found during the remaining follow-up period. For all soldiers both plasma levels of PIINP and PINP declined from day 0 to day 1 by median 32%, \( P < 0.01, n = 10 \). No significant changes with time for either of the two collagen formation markers were found hereafter.

Chest radiographs and arterial blood gas analyses remained normal for all the soldiers during follow-up.

**Discussion**

We have demonstrated a significant decrease in DLCOcorr, TLC and Dl/Va after modest open-air exposure to ZCS with a corresponding increase in serum levels of fibrinogen and zinc. These findings indicate that sufficient amounts of ZCS must have passed deeply enough into the lower respiratory tract to induce a quantifiable reduction in lung function.

Preliminary data and statistics on changes in DLCOcorr after exposure to ZCS from the present study have already been published (17). The present study is an expanded version with prolonged follow-up, improved computed statistical analyses and extended blood sample analyses.

Gas transfer for carbon monoxide after exposure to ZCS has only been described previously in three singular cases. One was found normal (11), another had a slight reduction in DLCO 4 months after exposure (15) and the third one showed moderate to severe reduction 2 weeks after exposition with recovery after 2-3 months (16). A ZCS bomb contains hexachlorethane (\( \text{C}_6\text{Cl}_6 \)), zinc oxide (ZnO) and calcium silicide (\( \text{CaSi}_2 \)) along with minor amounts of aluminium, magnesium and ammonium chloride. When ignited these components form mainly zinc chloride (\( \text{ZnCl}_2 \)), which again in aqueous solution forms hydrochloric acid (HCl) and zinc oxychloride (\( \text{ZnClO}_2 \)) (4). These three chemicals are all corrosive. Also minor amounts of phosgene (\( \text{COCl}_2 \)), carbon monoxide (CO) and polyaromatic hydrocarbons are produced, but the pulmonary and toxic impact of these compounds is generally considered to be of little or no importance in this context (25).

In confined spaces an ignited smoke bomb rapidly absorbs all available moisture from the air. In such a case the main component of the smoke will be zinc chloride in minute sized particles ranging from 0.01 to 25\( \mu \) which may pass deep into the respiratory tract (26). With increasing air humidity successively larger amounts of zinc chloride will be hydrolysed into hydrochloric acid and zinc oxychloride. The hydrochloric acid absorbs comparably more water and forms larger particles mainly deposited in the upper respiratory tract (27).

In rats ZCS induces pulmonary oedema, alveolitis and subsequently fibrosis (28). The pathological findings after fatal cases in man are similar. They include extensive interstitial and intra-alveolar fibrosis, diffuse microvascular obliteration and widespread occlusion of the pulmonary arteries (29). The progression of ARDS is suggested to be mediated through a programmed release of mediators from recruited and activated inflammatory cells and stimulation
of mediator cascades that include cytokine interactions (13).

The increase in serum levels of fibrinogen and zinc and the decline in DLCOcorr, TLC, Dl/Va and to a lesser extent MEF25 is compatible with an ulcerative and fibrotic process in the lung alveoli and smaller bronchioli with a delayed onset and an apparent maximum at 4 weeks after exposure (30). However, the modest symptoms of the soldiers did not justify attempts to verify this by histology neither by biopsy nor by bronchoalveolar lavage. The following healing response seems slow, and one cannot rule out the possibility of permanent damage from the present data. The slight increase in VC and FVC found 2 weeks after exposure can be explained by adaptation to the test procedure. It is also noteworthy that the reduction VC and FEV1 described in patients with heavy exposure to ZCS was not demonstrable in the present material. This may indicate that DLCOcorr, TLC and Dl/Va are more sensitive procedures in such cases with mild exposure. Although a sufficiently matched control group was not obtainable due to the acute circumstances of the study, we are confident that the observed changes are not due to circadian variations or lung function technicians.

YKL-40 is presumed to function in tissue remodelling and serum YKL-40 levels are elevated in patients with active rheumatoid arthritis (20), in patients with liver fibrosis (21) and in patients with recurrent breast cancer and metastases to bone and viscera (31). YKL-40 is secreted by human macrophages (32) and is a matrix protein in specific granules of human neutrophils. The early and significant rise in serum levels of YKL-40 may signal early tissue damage. The increase in YKL-40 may have been larger if the patients had not been treated with prednisolone, since glucocorticoid administration to patients with non-infectious inflammatory diseases leads to reductions in serum YKL-40 within 1 day (Julia S. Johansen, personal communication). The decline found from day 0 to day 1 for PIIINP and PINP is most probably due to the glucocorticoid treatment. The lack of significant changes in PIIINP and PINP does not rule out their importance in this context as at least PIIINP already has been shown to be elevated in ARDS (33,34). The lower numbers of blood samples for analysis of those markers may have hidden important information on the degree of fibrosis or simply reflect the low degree of exposure.

Since peak levels of serum zinc appear late in the follow-up period and are merging peak levels of fibrinogen, zinc level in serum seem to act as an acute phase reactant rather than expressing the initial degree of exposure.

Prolonged observation after exposure is in general recommended in the presence of diffuse infiltration on chest radiograph, pyrexia, leucocytosis and elevated levels of zinc in urine or blood. Such findings may indicate exposure of zinc chloride or zinc oxychloride to the alveoli. Recently, the immediate damage to lung parenchyma has also been determined by technetium-99m DTPA radioaerosol inhalation lung scintigraphy (35). Since none of the exposed soldiers from this study developed ARDS one may only speculate that the development of acute phase reactants and DLCOcorr after ZCS exposure may contribute to early diagnosis of ARDS. But it is important to point out that even modest exposure to ZCS leads to quantifiable changes in both lung function and acute phase reactants. This finding justifies the inclusion of phase reactants and determination of DLCOcorr when monitoring patients after exposure to ZCS.

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References


