

IMPAIRED RESPIRATORY MUSCLE FUNCTION IN CHEMICAL PLANT WORKERS PRODUCING CHLORFENVINPHOS

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Konieczny B, Kossmann S, Makuch M: Impaired respiratory muscle function in chemical plant workers producing chlorfenvinphos. *Ann Agric Environ Med* 1999, **6**, 21–25.

Abstract: All employees of a chemical plant division producing chlorfenvinphos were studied, i.e. 35 males aged 25–57 years (mean 42.1); their employment period ranged from 1–15 years (mean 9.0). Chronic bronchitis was diagnosed in 13 workers (37.1%). Mean air chlorfenvinphos concentrations in the work environment estimated with gas-liquid chromatography were from 0.0008–0.0018 mg/m³ (maximum allowable concentration according to Polish standards is 0.01 mg/m³). The activity of erythrocyte acetylcholinesterase was similar to that observed in people who were not exposed to chemicals, however, a slightly lowered activity of plasma cholinesterase in the studied population was evidently the result of mild liver impairment. Spirometric investigations performed in the studied workers revealed slight alterations manifested by increased intrathoracic gas volume (ITGV) (the value of the index was 138.6% of the mean value, 24 workers with an abnormally high index), as well as by decreased specific airway conductance (sGaw); its mean value in the studied group was 58.5% of the mean standard (11 people showed an abnormal index). Substantial functional changes were found in the respiratory muscles. Maximal inspiratory pressures (MIP = 97.2 ± 28.3 cm H₂O) as well as maximal expiratory pressures (MEP = 113.9 ± 44.2 cm H₂O) in the studied group were significantly lower ($p < 0.01$) as compared to those observed in the control group (MIP = 120.7 ± 31.7 ; MEP = 154.4 ± 40.2 cm H₂O) of 22 males having similar cigarette smoking habit, without occupational exposure to chemicals. It was also found that the people who had worked for more than 10 years under conditions of exposure to chlorfenvinphos showed significantly lower ($p < 0.05$) values of maximal inspiratory pressure (87.2 ± 28.06 cm H₂O, n = 17) compared to the workers whose period of employment was shorter than 10 years (106.6 ± 26.8 cm H₂O, n = 18). The two groups were comparable with regard to age and smoking habits. The values of maximal expiratory pressures were similar in both groups. No essential disturbances in neuro-muscular transmission were observed; only in 3 workers (8.5%) the electrostimulating myasthenic test showed some disturbances in neuro-muscular transmission. It seems that respiratory muscles impairment in humans exposed to chlorfenvinphos results from changes in the metabolism and structure of muscles, and partly from lung hyperinflation.

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Key words: lungs, spirometry, respiratory muscles, phosphoroorganic pesticides, chlorfenvinphos, occupational exposure, chemical plant workers, health effects, repetitive nerve stimulation test.

INTRODUCTION

Farmers often complain of respiratory disorders [28], and pesticide exposure is one of several factors contributing

to impaired respiratory function in agricultural workers [27]. Our investigations of chemical plant workers producing organic phosphorus pesticides [12] and chlorfenvinphos [8] showed spiropgraphic signs of small airways disease

and pulmonary emphysema. Efficient respiratory muscles are necessary for normal functioning of the respiratory system. Disturbances of neuromuscular function in organophosphate workers were shown [5, 14, 25], and our investigations in chemical plant workers exposed to chlorfenvinphos confirmed decreased motor nerve conduction velocity [24].

Rats subacutely intoxicated with selected organophosphates, among them chlorfenvinphos, were found to have degenerative changes in diaphragmatic muscle fibres [4], and chronic chlorfenvinphos intoxication caused skeletal muscle atrophic lesions in the rats [6]. One can expect that the respiratory muscle dysfunction contributes to impaired lung function in humans exposed to chlorfenvinphos.

The aim of the present work was to determine whether impaired respiratory muscle function could take part in the development of ventilatory dysfunction in the workers employed in the production of chlorfenvinphos.

MATERIALS AND METHODS

All the staff members of a chemical plant division producing chlorfenvinphos were studied, i.e. 35 males aged 25–55 years (mean 42.1 ± 7.5), duration of employment 1–15 years (mean 9.0 ± 4.3); 22 were smokers, the smoking index: 17.3 ± 11.6 pack-years. In 13 of the studied workers (37.1%) chronic bronchitis was diagnosed according to the BMRC questionnaire [19]. None of the workers had atopic airways disease.

Air chlorfenvinphos concentration in the production area was estimated in the factory laboratory using gas-liquid chromatography according to the Polish standard [17]. The results, given as 8-hour weighed average concentration, were 0.0008–0.0018 mg/m^3 , and they did not exceed the maximum allowable concentration for chlorfenvinphos of 0.01 mg/m^3 [20]. The ambient air was sampled by means of passing 50–100 l of the air through a glass column absorber packed with silica gel at a sampling velocity of 2 l/min.

Spirometry was performed using the Jaeger Masterlab spirometer and the following parameters were estimated: vital capacity (VC), forced expiratory volume in one second (FEV_1) and FEV_1/VC ratio ($\text{FEV}_1\%$), maximal expiratory flow at 25% VC ($\text{MEF}_{25\%}$), peak expiratory flow (PEF), gas transfer factor (TLCO), specific airways conductance (sGaw), intrathoracic gas volume (ITGV) and the ratio of residual volume to total lung capacity (RV/TLC). The predicted normal values were proposed by Quanjer [18], however, the values for sGaw were suggested by Briscoe and DuBois [3]. Maximal static inspiratory (MIP) and expiratory (MEP) mouth pressures at the functional reserve capacity and total lung capacity were measured using Siemens Siregnost FD 88 spirometer according to Black and Hyatt [2]. The predicted normal values were those of Walczak and Małkosa [26]. The results were compared with those of a control group of 22 healthy men, aged 20–62 years (mean

39.6 ± 12.3), without occupational exposure to chemicals. 12 (54%) subjects were smokers; the smoking index was 15.7 ± 9.5 pack-years. In 22.7% of the control subjects simple chronic bronchitis was diagnosed.

The repetitive nerve stimulation test is considered to be a sensitive method for detection of neuromuscular transmission abnormalities [16]. This test was performed using the Dantec Counterpoint electromyograph with surface electrodes. In brief, the right ulnar nerve was stimulated at 30 sec. intervals with repeated submaximal electric stimuli during 0.2 ms with frequencies of 3, 10, and 20 Hz, and then four times with the frequency of 3 Hz; the compound muscle action potentials of the hypothenar muscle were recorded, and the difference between 1st and 5th contraction amplitude was estimated. Normal amplitude differences were obtained in 30 healthy males, aged 35–52 years (mean 47.5 ± 8.7), residents of the region, without occupational exposure to chemicals.

Red blood cell acetylcholinesterase (AChE) and plasma cholinesterase (ChE) activity was determined spectrophotometrically using the modified Ellman's method [15]. Normal values were obtained in 33 healthy males, aged 20–55 years (mean 33.1 ± 12.9), residents of the region, without occupational exposure to chemicals.

For statistical analysis, the unpaired Student's t-test was applied, probability values of less than 0.05 were considered statistically significant.

RESULTS

Spirometric investigations of the workers employed in the production of chlorfenvinphos showed an elevated thoracic gas volume and decreased air conductance (Fig. 1). Maximal inspiratory and expiratory pressure

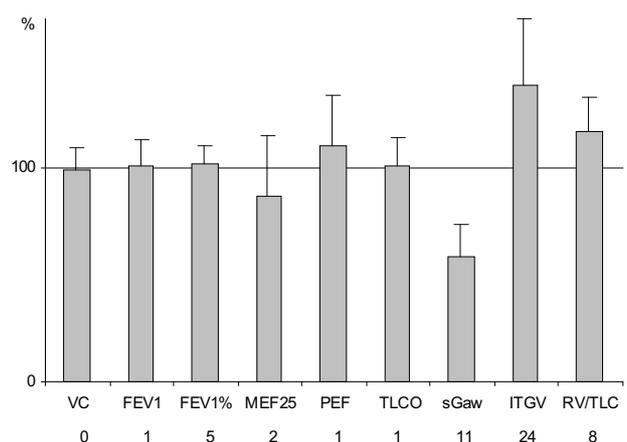


Figure 1. Spirometric indices (mean \pm S.D.) in the study group: percentage of predicted values. At the bottom of each bar the number of values beyond normal range found in 35 workers is given (VC- vital capacity, FEV_1 - forced expiratory volume in one second, $\text{FEV}_1\%$ - FEV_1 as a percent of vital capacity, MEF_{25} - maximal expiratory flow at 25% of the forced vital capacity, PEF- peak expiratory flow, TLCO- gas transfer factor, sGaw- specific airway conductance, ITGV- intrathoracic gas volume, RV/TLC- ratio of residual volume to total lung capacity).

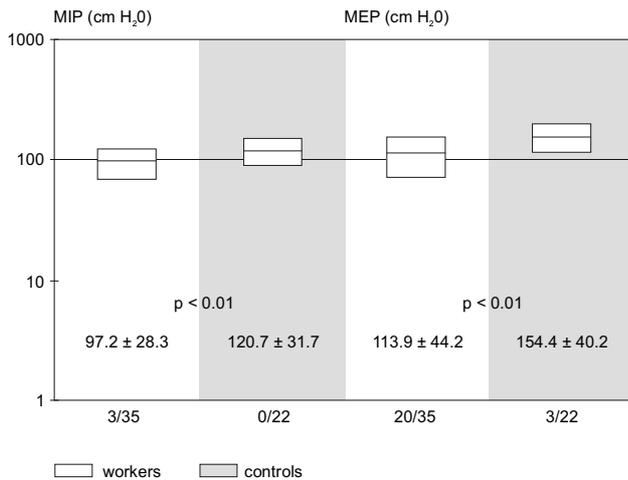


Figure 2. Absolute values of maximal inspiratory (MIP) and expiratory (MEP) pressure in workers and controls. At the bottom of each bar the number of values beyond normal range is given.

volumes in the studied population were significantly lower ($p < 0.01$) compared to the controls (Fig. 2).

People professionally exposed to chlorfenvinphos were more frequently found to have abnormally low values of maximal inspiratory pressures (3 workers - 8.6%) and expiratory pressures (20 workers - 57.1%), whereas in the control group (Fig. 2) only the expiratory pressure did not reach normal values in 3 individuals. The mean value of maximal inspiratory pressure in the workers producing chlorfenvinphos, whose employment period was longer than 10 years (17 subjects, mean age 44.0 ± 7.5 years), was 87.2 ± 28.1 cm H₂O, and it was significantly lower ($p < 0.05$) than the value observed in the workers whose employment period was shorter than 10 years (18 subjects, mean age 40.4 ± 7.2) where the mean MIP value amounted to 106.6 ± 26.8 cm H₂O. The age difference between the two groups was insignificant.

DISCUSSION

Effect of air contamination in the work environment may impair the mechanics of respiration in different ways. Our previous research showed an increased incidence of chronic bronchitis among the workers employed in the production of pesticides, as well as frequent occurrence of impaired pulmonary ventilation, manifested by an obturation syndrome and spirometric features of pulmonary emphysema [8, 9, 12]. In the present study the exposure of workers was small, air chlorfenvinphos concentration in the work environment did not exceed the maximal allowable concentrations, and consequently erythrocyte AchE activity was similar to that in the control group.

Lower values of serum (nonspecific) cholinesterase activity found in the workers employed in the production of chlorfenvinphos probably result from an impaired function of the liver (the site of ChE production) in these

subjects. Discrete features of liver function impairment were shown [11].

Slight impairment of lung ventilation, manifested by decreased specific airway conductance, might indicate bronchial inflammatory changes. These findings are in accordance with the results of questionnaire investigations which showed increased incidence (37.1%) of chronic bronchitis in the studied population compared to the control group (22.7%).

It is very likely that this increase was not caused by different exposure to cigarette smoke, as the percentage of smokers and the smoking index in the control group were similar to those in the studied group. The increase of ITGV and RV/TLC indices, frequently observed in spirometric investigations, was found in pulmonary hyperinflation and emphysema. Earlier functional studies in people professionally exposed to chlorfenvinphos [8] showed modification of elastic resistances of the respiratory system, manifested by decreased elastic recoil pressure and increased static lung compliance, i.e. the changes observed in pulmonary emphysema. Since diffusing capacity for CO (TLCO) as well as end-expiratory flows were not markedly altered, it is possible that the features of hyperinflation rather than emphysema were predominant in the studied population (Fig. 1).

The present study shows weakness of respiratory muscles in the workers employed in the production of pesticides as compared to controls (Fig. 2). This was manifested by lower maximum pressures in the oral cavity during inspiration (MIP) and expiration (MEP). Weakness of the respiratory muscles may be due to pathologic changes in muscles, fatigue of muscles caused by overloading them, as well as to impairments of the nervous system.

In experimental subacute exposure of animals to chlorfenvinphos Gajewski *et al.* [4] found degenerative changes in the rat diaphragm fibres. Morphometric investigations of the muscles of animals chronically exposed to chlorfenvinphos showed atrophic changes of fibre structures [6].

Free oxygen radicals take part in the impairment of the muscle cell function [1, 23]. Pathologic processes leading to increased production of free radicals are connected with alterations in the respiratory muscles. When free radicals attack polyunsaturated fatty acids of cell membranes, they impair them. They may also interfere with substantial enzymatic cell processes. It has been shown that intensification of lipid peroxidation (effect of free radicals) produced fatigue of diaphragm muscles; earlier administration of free radical scavengers reduced the development of fatigue [23].

Our earlier investigations of humans professionally exposed to chlorfenvinphos showed an increased concentration of serum lipid peroxidation products (TBARS), along with lowered activity of the enzymes taking part in the defense system against free radicals damage (erythrocyte superoxide dismutase and catalase) [10]. Chlorfenvinphos may also interfere with energetic

processes of muscles. Cytochemical studies of rats intoxicated by chlorfenvinphos showed disturbances of the oxygen-generated energy production process in skeletal muscles (the diaphragm included) [7]. Impairment of muscle fibres was associated with enhanced anaerobic glycolysis.

The mechanisms responsible for muscle weakening in the studied workers were less feasible because the changes of spirometric indices were relatively low, and lung hyperinflation should probably be connected with respiratory muscle weakness. An increased intrathoracic gas volume (ITGV) produces flattening of the diaphragm, which in turn results in shortening of muscle fibres. Reduction of length of the optimal muscle fibre weakens the muscle force [21, 22].

Changes in the nervous system responsible for coordination of muscle function could also be one of the factors reducing the respiratory muscle force, and disturbances in neuro-muscular transmission may impair muscle function [5, 16]. Our previous investigations of the workers exposed to chlorfenvinphos showed decreased motor nerve conduction velocity [24]. Disturbed neuro-muscular transmission and reduced respiratory muscle force were found in workers exposed to various classes of pesticides: triazines, carbamates, dithiocarbamates, carbendazim, captan, dodine, 2,4-D, pyrethroids [13].

The present study shows that the changes in neuro-muscular transmission were infrequent (found only in 3 workers), and therefore it can be presumed that this mechanism does not play an important role in the weakening of respiratory muscles. Since disturbances in neuro-muscular transmission are usually general, and electro-neurophysiological investigations of respiratory muscles are technically difficult, the ulnar nerve and the hypothenar muscle were therefore used in our studies [16].

It seems that the diminished respiratory muscle force depends mainly on the direct effect of chlorfenvinphos on striated muscles.

CONCLUSION

In the light of the above findings it can be postulated that impairment of the respiratory muscle function in the workers producing chlorfenvinphos was partially caused by lung hyperinflation as well as by changes in the metabolism and muscle structure. Reduction of the respiratory muscle strength is one of the factors responsible for impaired function of the respiratory system in humans chronically exposed to chlorfenvinphos.

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