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Bronchial responsiveness and work-related asthma in aluminium potroom workers: effect of removal from exposure

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Bronchial responsiveness and work-related asthma in aluminium potroom workers: effect of removal from exposure. V. Søyseth, J. Kongerud, J. Boe, T. Fonneland.
ABSTRACT: Twelve subjects relocated from aluminium potrooms due to work-related asthma were followed up for 2–27 months (median 23 months). Repeated post-relocation examinations (numbering 3–7, median 6) of methacholine challenge, forced expiratory volume in one second (FEV_1), eosinophil cell count and respiratory symptoms were carried out at regular intervals. At the time of relocation, bronchial hyperresponsiveness (provoking concentration producing a 20% fall in $FEV_1(PC_{20}) \leq 8.0$ mg·ml^{-1}) was found in eight of the subjects.
During the follow-up period a twofold increase in PC_{20} was found in 7 of the 8 subjects who had $PC_{20} < 8.0$ mg·ml^{-1} at the time of relocation. There was an improvement of symptoms but no improvement in FEV_1 or decrease of eosinophils during the follow-up examinations.
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Aluminium is produced by electrolysis of alumina in electrolytic cells (pots). The electrolyte consists of cryolite which dissolves alumina. Dust and gases containing fluorides, SO_2, polycyclic aromatic hydrocarbons and minor amounts of metals such as chrome and vanadium are emitted to the work environment during the process.

Aluminium potroom asthma has been described in several reports [1]. The cause(s) is (are) not known. Two possible mechanisms have been suggested: 1) provocation of asthma in subjects with pre-existing bronchial hyperresponsiveness (BHR) due to high levels of irritants such as hydrogen fluoride or SO_2; 2) induction of airway inflammation (AI) by agents in the potroom atmosphere. In the former case, one should not expect any improvement in bronchial responsiveness (BR) after removal from exposure. If potroom asthma is mediated by AI, and if this inflammation is reversible, one would expect a decrease in BR in subjects relocated from the potrooms because of this disorder. In follow-up studies of relocated workers with red cedar asthma and isocyanate asthma, both improvement and persistent BHR have been described [2, 3]. These studies have indicated that the duration of exposure is negatively associated with the degree of improvement.

The prognosis of subjects who leave the potrooms because of work-related asthma is not known. Some reports indicate that the workers still have symptoms after removal from exposure [4, 5]; however, both improvement and persistence of BHR have been described [5, 6]. In a review article Newman Taylor [7] concluded that a high proportion of those who develop occupational asthma exhibit respiratory symptoms and BHR persistence for several years after contact with the initiating agent has ended.

Recent research has shown that eosinophils take active part in the pathogenesis of asthma [8]. An increased number of eosinophils in venous blood has been found in those asthmatics who develop late reactions after allergen challenge, compared with those asthmatics who only show immediate reactions [9]. Furthermore, an increased number of eosinophils in venous blood has been associated with potroom asthma [10].

In this paper, we describe the follow-up of 12 subjects relocated from the potrooms because of work-related asthma. The aim of the study was twofold: 1) to describe BR at the time of relocation; and 2) to investigate whether BR changed after relocation. We also wanted to examine blood eosinophil cell count, respiratory symptoms and FEV_1 during the follow-up period.

Subjects and methods

The study was conducted between December 1986 and July 1989, at an aluminium smelter located in western Norway with 1,800 employees, including 380 potroom-workers. During this period, 13 subjects contacted the plant's physician (VS) because of respiratory symptoms and wanted to be relocated from the potrooms. The subjects underwent a clinical examination including their history of respiratory symptoms and chest auscultation. Work-related asthma was defined as the combination of chest tightness and wheezing improving on days away from work. Thus, the diagnosis of work-related asthma was made without knowledge of FEV_1, methacholine challenge and eosinophil cell count. Of the 13 subjects, 12 (11 males and 1 female) were suspected to have work-related asthma. One of the subjects was suspected of having acute bronchitis and was not included in the study. All subjects gave their informed consent to participate in the survey.

There were five current smokers, five lifelong non smokers and two former smokers. None of the subjects changed their smoking habits during the study. The median age was 37 yrs (range 23–56 yrs). Nine subjects were treated with β_2-agonists and two of these were treated intermittently with inhaled corticosteroids. Three subjects required no medical treatment.

A skin prick test of five common aero-allergens (dog epithelium, common silver birch, timothy grass, mugwort and house mite) was performed on each individual [11]. A positive test, defined as at least one wheal larger than the histamine reference, was found in one subject.

The workers were examined on their first day of relocation and re-examined 1.5, 3, 6, 12, 18 and 24 months later. The median follow-up time was 23 months and the median number of tests was six (table 1). Eight of the subject (nos 2, 4, 6–10 and 12) were still exposed to irritants such as SO_2 and dust in other areas of the plant *i.e* the carbon plant or the cast house, during follow-up. The remaining subjects were relocated to areas that could be regarded as clean or they left the plant.

A dry bellow spirometer (Jones Pulmonaire, Jones Medical Instruments Co., Oak Brook, Illinois, USA) was used for measurements of FEV_1. The subjects were invited to take part in the study if their FEV_1 was > 1.5 *l* or at least 50% of predicted [12].

Methacholine challenge testing was performed as suggested by Cockcroft *et al.* [13]. The same nebulizer was used throughout the study and it was calibrated to give an output of 0.13 $ml\cdot min^{-1}$. Aerosols were inhaled by tidal breathing for 2 min, doubling the concentration of methacholine at 5 min intervals, starting at 0.125 $mg\cdot ml^{-1}$. The test was discontinued when the FEV_1 had fallen by >20% from the pretest value or when a methacholine concentration of 32.0 $mg\cdot ml^{-1}$ was reached. The response was expressed as the provoking concentration of methacholine to cause a 20% fall in FEV_1 (PC_{20}) and was obtained by linear interpolation on a logarithmic scale on the basis of the data from the two last points on the non-cumulative dose-response curve. If FEV_1 fell by more than 20% at the lowest concentration, PC_{20} was calculated from the formula:

$$[(\text{methacholine concentration}) \times 20]/[\%\text{fall in } FEV_1]$$

as suggested by Cockcroft *et al* [13]. The first test was performed at the time of relocation. Thus, each subject (except one) had been exposed to potroom atmosphere for 6–7 h prior to the first test. In one subject (no. 4) the first test was postponed for four days because of asthmatic symptoms. In the case of upper respiratory infection during the last 6 weeks prior to a test, the tests were postponed for 6 weeks. All tests were performed between 12.00 a.m and 01.30 p.m.

Before each test the subjects were asked to record their symptoms on a self-administered questionnaire

Table 1. – Distribution or duration of employment duration of symptoms*, work exposure* (to dust and total fluorides), numbers of tests and follow-up time in relocated aluminium potroom workers

Subject no.	Duration of employment yrs	Duration of symptoms yrs	Exposure Dust $mg\cdot m^{-3}$	Exposure Total F $mg\cdot m^{-3}$	Follow-up Tests n	Follow-up Time months
1	37.0	2.5	2.2	0.2	7	25
2	26.5	14.0	1.7	0.4	7	25
3	31.6	6.7	3.2	0.7	5	27
4	15.3	3.5	3.1	0.7	5	12
5	9.6	2.2	3.8	1.1	7	19
5	23.4	1.2	1.1	0.4	6	21
7	4.1	0.8	2.2	0.7	5	15
8	8.2	5.0	2.7	0.7	7	27
9	8.3	0.7	2.3	0.5	7	27
10	3.9	1.2	2.1	0.5	5	12
11	0.8	0.3	2.2	0.3	3	2
12	4.5	2.5	2.5	0.3	7	25
Median	9.0	2.4	2.2	0.5	6	23
IQR	4.3–25	0.8–5.9	2.1–2.9	0.4–0.7	5–7	14–26

*at the time of relocation; IQR: interquartile range; F: fluorides.

(dyspnoea, wheezing and cough), stating severity and frequency in the time interval since the last test. These questions were answered on a graded scale (0–3).

Venous blood was taken just before methacholine challenge testing. Eosinophil cell counts were performed with a Fuchs-Rosenthal counting chamber [14] by an observer without knowledge of the result of the methacholine challenge test.

Exposure assessments for different working tasks have been carried out regularly since 1986 by measurements on 8 h samples [15]. A geometric mean of dust and total fluorides was calculated for each job category of the 12 subjects prior to relocation (table 1).

Statistical analysis

Wilcoxon's non-parametric signed rank test for paired observations was used for comparing the results of the same individual at the time of relocation and at the end of the follow-up. If PC_{20} was >32.0 mg·ml^{-1} BR was ranked by according the (FEV_1) post test at 32.0 mg·ml^{-1} methacholine. More than twofold changes in PC_{20} between two occasions were regarded as significant [16]. Spearman rank correlation was also used.

Results

In table 2 we have compared PC_{20}, eosinophil cell count and FEV_1 for each subject at relocation (First) and at the end of the follow-up (Last). One subject (no. 7) had a PC_{20} >32.0 mg·ml^{-1} on relocation. In nine of the remaining 11 subjects PC_{20} increased more than twofold. The median PC_{20} of the whole group was 4.4 mg·ml^{-1} at relocation. After 1.6 months (second test) the median-PC_{20} had increased to 9.7 ($p>0.05$), and at end of follow-up the median-PC_{20} was >32.0 mg·ml^{-1} ($p<0.01$) (table 2). The median-PC_{20} and PC_{20} for each subject is shown in figure 1. The Spearman's rank correlation between PC_{20} at relocation and end of follow-up was 0.59 ($p<0.05$). In nine of the subjects the number of eosinophils decreased between the first and the last test but the changes were not significant, and the median of eosinophils decreased from 246 to 235 × $10^6 \cdot l^{-1}$ (table 2). The median of FEV_1 was unchanged. Between the second and the last test the median symptom score fell from 7 to 1.5 ($p<0.05$) (table 2). A decrease in symptom- score was found in seven of the 12 subjects and one subject was already symptom free at the second test (no. 7).

Two subgroups of the population could be identified: subjects with short duration of employment (<10 yrs, median 4.5 yrs), and those with long duration of employment (>15 yrs, median 26.5 yrs). The latter group was characterized by lower FEV_1 than the former, and three out of four of those who had PC_{20} <16.0 mg·ml^{-1} on relocation still had PC_{20} <16.0 mg·ml^{-1} at the end of the follow-up. None of the six out of seven subjects with short duration of employment, who had a PC_{20} <16.0 mg·ml^{-1} on relocation, had PC_{20} <16.0 mg·ml^{-1} at the end of the follow-up.

Table 2. – Changes in FEV_1 (%pred), PC_{20}, eosinophils and symptom score between the first (second regarding symptom score) and the last test* in each subject after relocation

Subject no.	FEV_1 First l	First % pred	Last l	Last % pred	PC_{20} First mg·ml^{-1}	PC_{20} Last mg·ml^{-1}	Eosinophils First ×$10^6 \cdot l^{-1}$	Eosinophils Last ×$10^6 \cdot l^{-1}$	Symptom score Second	Symptom score Last
1	2.6	(74)	2.5	(70)	4.6	24.7	131	50	8	8
2	1.5	(40)	1.5	(41)	0.1	6.1	694	406	14	9
3	2.6	(62)	2.5	(61)	19.3	>32.0	269	238	3	4
4	2.0	(55)	2.0	(56)	2.1	1.8	169	231	6	0
5	3.1	(99)	3.1	(99)	4.2	>32.0	100	81	6	0
6	3.5	(82)	3.4	(80)	0.3	2.8	125	56	1	2
7	5.2	(112)	4.9	(106)	>32.0	>32.0	244	119	0	0
8	3.9	(96)	3.9	(96)	1.0	>32.0	362	75	9	0
9	5.2	(94)	4.9	(90)	15.9	>32.0	206	294	16	12
10	5.3	(107)	5.3	(108)	9.7	>32.0	250	381	9	0
11	3.6	(80)	4.4	(97)	3.2	>32.0	325	294	8	1
12	4.7	(87)	4.7	(89)	7.3	28.0	757	475	4	4
Median	3.6	(85)	3.8	(85)	4.4	>32.0	246	235	7	1.5
LQ	2.6	(68)	2.5	(66)	1.5	15.4	150	78	3.5	0
UQ	4.9	(98)	4.8	(99)	12.8	>32.0	344	338	9	6
p-value		0.95			<0.01		0.15		<0.05	

LQ: lower quartile; UQ: upper quartile; FEV_1: forced expiratory volume in one second; PC_{20} provoking concentration producing a 20% fall in FEV_1 from baseline value.*: end of follow-up.

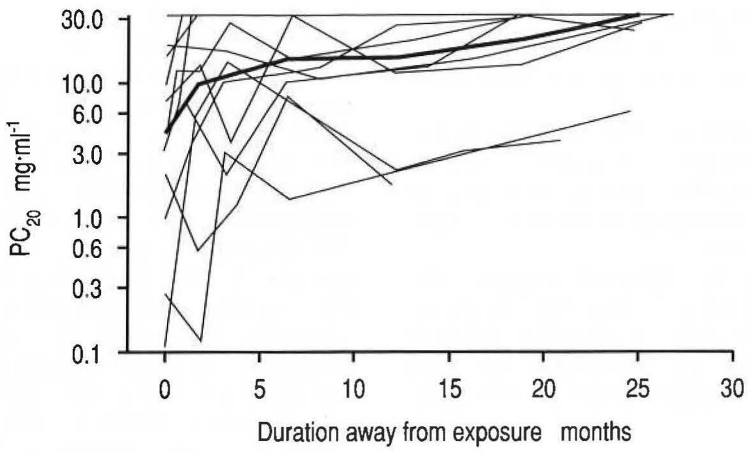

Fig. 1. – PC_{20} of each subject and the median of PC_{20} (thick line) in the follow-up of 12 aluminium potroom workers relocated due to work-related asthma. PC_{20}: provoking concentration producing a 20% fall in FEV_1 from baseline value; FEV_1: forced expiratory volume in one second.

Discussion

In 12 potroom workers who were relocated because of work-related asthma, median-PC_{20} increased about tenfold during a 2 yr follow-up period.

This observation could be explained by "regression to the mean". However, the median duration of symptoms before relocation was 2.4 yrs, indicating that their asthma was stable at the time of relocation. As BR at relocation and end of follow-up was positively correlated, the decrease in BR could not merely be explained as a "regression to the mean" effect [17]. An increase in PC_{20} among relocated aluminium potroom workers was also found by O'Donnell *et al.* [5]. Persistent BHR was found after cessation of exposure in the majority of workers relocated because of occupational asthma induced by red cedar [2], isocyanates [3] and aluminium-salt [18]. In one of these studies [3], the duration of exposure was longer and comparable with the workers in the present study who had been exposed for more than 15 yrs. The relationship between BR at end of follow-up and exposure duration is also supported by our data. In the study reported by Simonsson *et al.* [18], the exposure levels to aluminium fluorides were probably higher than those found in the present study. Thus, the change in BR after cessation of exposure seems to be related to the level and time span of exposure. The rate of improvement seems to be faster in these workers than in those with asthma caused by known sensitizers such as red cedar [2]. In the study of Chan-Yeung *et al.* [2], a three-fold increase in PC_{20} was found after 30 months in subjects who became asymptomatic. We found a threefold increase in PC_{20} after 6 months, including all of our subjects.

In 1988, we conducted a cross-sectional study of BR among potroom workers at the same plant using the same staff and equipment as in this study [19] . BHR ($PC_{20} \leq 8$ mg·ml^{-1}) was found in 5% of the total workforce and in 19% of those with work-related asthmatic symptoms. Thus, BR to methacholine among relocated workers at the inclusion to the present study was markedly increased, compared to the active workforce in the cross-sectional study. This indicates that the severity of symptoms seems to be related to the degree of BR. This was also described elsewhere [20].

A significant decrease in BR was observed in the follow-up period. This decrease was already observed after 1.8 months. Temporary increase in BR following specific provocation to red cedar and isocyanates in subjects with occupational asthma has been reported [21, 22]. Studies of bronchoalveolar lavage have suggested that the late reaction is associated with AI that follows the increase in BR induced by specific challenge [23]. The observed decrease in BR by cessation of exposure could be explained by remission of AI after removal from exposure. Thus, the hypothesis that asthma in these workers only was provoked by irritants in subjects with pre-existing BHR is unlikely. The agent(s) inducing BHR under these conditions is (are) not known. In our previous study [19], a positive association between respiratory symptoms and fluoride exposure was found but there was no association between BR and fluorides or dust [24]. As fluoride and SO_2 provoke bronchoconstriction in subjects with BHR, this finding is likely to be biased by selection. Thus, the relationship between BR and these exposures should be examined in a longitudinal study.

The levels of occupational exposure were not higher among relocated workers than among the active workforce [24]. A history of accidental high exposures was not obtained in any of the subjects. Thus, their symptoms and BR cannot be explained in terms of reactive airway dysfunction syndrome (RADS) [25].

The changes in symptom score and eosinophil cell count were minimal, although significant for symptom score. As peripheral eosinophil cell count is an imprecise indicator of AI, it was desirable to have data from bronchoalveolar lavage. However, this was not possible for practical reasons. There was no improvement in FEV_1 during the follow-up. Thus, the improvement of BR was not followed by a corresponding improvement of other indices of asthma. This might indicate that the improvement of asthma was incomplete.

In conclusion, this study indicates an improvement of BR among aluminium potroom workers after relocation due to work-related asthma. A similar improvement was not observed regarding respiratory symptoms, FEV_1 or eosinophil cell count. This shows that the effect of relocation on the prognosis of work-related asthma among aluminium potroom workers is unclear.

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