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Case Report

Asthma caused by potassium aluminium tetrafluoride: a case series

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Abstract: The objective of this study is to describe a case-series of potassium aluminium tetrafluoride ($KAlF_4$)-induced occupational asthma (OA) and/or occupational rhinitis (OR). The study involves five patients from a heat-exchanger production line who were examined (including specific inhalation challenge tests) for suspected OA and/or OR caused by a flux containing almost 100% $KAlF_4$ − with fluorides' workplace air concentrations ranging between 1.7 and 2.8 mg/m^3. No subject had a previous history of asthma. All five patients had a positive specific challenge test (three patients were diagnosed with OA alone, one with OR and one with both OR and OA). At the follow-up visit, after three years on average, all patients needed permanent corticosteroid therapy (four topical, one oral). After elimination from the exposure, only one of the observed subjects gave an indication of an improvement, two subjects stabilized and two worsened. Our case series focuses on the correlation between patients' exposure to fluorides in air-conditioner production and the subsequent occurrence of OR/OA. Currently, it is uncertain whether these OR/OA were caused by hypersensitivity or irritation.

Key words: Potassium aluminum tetrafluoride, Hypersensitivity, Irritation, Occupational asthma, Occupational rhinitis

Introduction

Fluorides are considered to cause occupational asthma in the 'potroom' context (aluminium production) by inducing bronchial hyperreactivity. Occupational exposure accounts for approximately 16% of asthma in adults of working age[1)]; moreover, OA is the most reported occupation-related lung disease in the industrialized countries[2)].

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Occupational asthma

According to a recent consensus, work-related asthma (ACCP Consensus Statement CHEST 2008) includes work-exacerbated asthma and asthma caused by work, defined as occupational asthma (OA). There are two categories of OA. The first category includes sensitizer-induced OA, caused by high molecular weight glycoproteins or low molecular weight chemicals. The second category includes irritant-induced asthma, caused by exposure to irritants at work. Irritant-induced asthma (IIA) is not limited to bronchial hyperreactivity following an acute exposure to irritant compounds (reactive airways dysfunction syndrome (RADS or Brooks syndrome)), but also includes

chronic exposure to irritants. Thus IIA can be divided into three groups: i) definite IIA, developing within a few hours after a single acute exposure to high-level concentrations of irritants; ii) probable IIA, developing after multiple symptomatic high-level exposures to irritants; and iii) possible IIA, occurring with a delayed onset after exposure to moderate levels of irritant substances[3].

Potassium aluminium tetrafluoride

Potassium aluminum tetrafluoride with a molecular weight of 142 g/mol (CAS number 60304-36-1) is used as a flux for brazing aluminium parts and joining aluminium sheets and other components. It occurs in the form of a white powder. Aluminium brazing is used in the air-conditioning production within the automotive sector, and the commercial and household production of electrical appliances, such as refrigerators. Exposure to $KAlF_4$ may also occur in the production of welding rods, glassware and roofing shingles.

In accordance with the producer's material safety data sheet (MSDS), exposure to $KAlF_4$ causes irritation to the eyes, nose, throat, mucous membranes and skin. After a longer period of exposure, irritation to the bronchi, chronic bronchitis and dermatitis, sore throat and nosebleed were also reported.

The objective of the paper

Five patients suspected of having occupational asthma (OA) or occupational rhinitis (OR) due to exposure to $KAlF_4$ powder were sent to our Department of Occupational Medicine between 2007 and 2012. This paper focuses on the description of the working conditions and main results obtained during the patients' first and follow-up examination, which took place after their removal from work approximately three years later.

Subjects and Methods

Five patients exposed to $KAlF_4$ flux for 6 yr on average (mean age 45.8 yr) were examined for suspected OA, OR or both. Four women worked as operators at a brazing line, which included the completion of aluminium blocks and the cleaning off all aluminium parts from $KAlF_4$ using a brush. Another patient, a serviceman, worked on the repairing of all equipment including the suction unit, where the exposure to $KAlF_4$ was supposed to be the highest. All workers were equipped with working suits, gloves and, during the periods of higher exposure to $KAlF_4$ (i.e. when the suction unit was out of order), with lightweight particulate respirators with exhalation valve. There were approximately 800 workers employed in the factory. About 300 workers were present in a construction hall during one shift. The hall was furnished with central ventilation and separate suction units at each working table. Air concentration of $KAlF_4$ measured (as fluorides) in the brazing line workshop in the year 2006 ranged from 1.7–2.8 mg/m^3, i.e. the Czech workplace air concentration limit for inorganic fluoride dust of 2.5 mg/m^3 was exceeded. After 2007, several preventive steps in the workplace were performed and concentration of $KAlF_4$ was reduced to 0.5–0.7 mg/m^3.

All the patients' cases were taken and examined by occupational health specialists. Tests and parameters taken during the patients' first hospitalization at the Department of Occupational Medicine were as follows: spirometry, non-specific bronchoprovocation tests with histamine or methacholine, and a specific inhalation challenge test (SIC) using $KAlF_4$ powder from the workplace. Following the recommendations of the European Respiratory Society[4], Master Lab and Master Screen (Jaeger, Germany) was used for the purpose of spirometry.

Non-specific bronchoprovocation tests were performed with methacholine or histamine, using the Asthma Provocation System APS[5] (Jaeger, Germany). The histamine test was performed with the inhalation of histamine in increasing concentration: 1 mg/ml (0.037 mg), 5 mg/ml (0.216 mg) and 10 mg/ml (0.4322 mg). The methacholine test was performed with the inhalation of 3.2% methacholine in increasing doses (0.05 mg, 0.35 mg, 1 mg, 1.5 mg, 1.5 mg, and 1.5 mg). A decrease in forced expiratory volume in one second (FEV_1) exceeding 20% of the baseline level was considered to be a positive result. Bronchodilatation test was performed using the inhalation of 400 µg of salbutamol and increase in FEV_1 by at least 15% after 30 min was considered as a positive result.

The 24-h variation of spirometric parameters (mainly FEV_1 and peak expiratory flow (PEF) was examined before the specific provocation tests to ensure that the spontaneous variation of FEV_1 and PEF in the subject without challenge does not exceed 20%[6]. This measurement was done because no placebo test was performed to confirm the stability of spirometric parameters at rest (without provocation).

The SICs were performed in a special exposure box, where patients simulated their work (i.e. brushing the $KAlF_4$ powder off aluminium parts—an exposure to approximately 100 mg of the powder) for 30 min. Air levels of $KAlF_4$ were not measured during the SICs. One of the patients was tested at the workplace (exposure lasting

Table 1. Characteristics of the patients, latency to first symptoms, duration of exposure and outcome after removal

Patient	Sex	Age	Smoking	Latency to first symptoms	Duration of KAlF4 exposure	Period between first examination (diagnostic) and follow up	Clinical evolution after removal
				yr	yr	yr	
1	male	62	no	4	7	3	worsening
2	female	39	yes	1	3.5	4	no change
3	female	62	yes	4	5	2	no change
4	female	33	no	2	6	3	worsening
5	female	33	yes	4	6	2	improvement

for two hours). Spirometry and rhinomanometry were performed prior and immediately after the test and at two hours, five hours and 24 h after the provocation tests or whenever patients' symptoms worsened.

One or more of the following results served as the criteria of positivity of bronchoprovocation test: (i) a reduction of FEV_1 of more than 20% compared to the baseline level before testing (main criterion); (ii) a reduction of the mean expiratory flow (MEF) at 25%, 50% or 75% of the forced vital capacity FVC (MEF_{25}, MEF_{50}, MEF_{75}, respectively), of more than 30% compared to the baseline level; and/or (iii) an increase of the total airway resistance R_{tot} by more than 100% compared to the baseline value and the symptoms (wheezing, dyspnoea, cough).

Occupational asthma was diagnosed when diagnosis of bronchial asthma was confirmed; the SIC was positive and 24 h variation of FEV_1 done before the SIC did not exceed 20%[7].

Occupational rhinitis was confirmed by rhinomanometry results and symptoms of rhinitis (i.e. watery secretion, itching, and/or snoring). Anterior rhinomanometry was performed by Rhinoscreen (Jaeger, Germany). Nasal flow (both right and left side) reduction of at least 40% in comparison to the baseline value was considered to be a positive rhinomanometry result. Nasal resistance (both right and left side) increase by at least 60% in comparison to the baseline value was considered to be a positive rhinomanometry result[8].

In addition, plasma levels of total immunoglobulin E (IgE, reference range 35–100 IU/ml) and eosinophilic cationic protein (ECP, reference range 0–24 ng/ml), were performed. If available, fractioned exhaled nitric oxide (FeNO)[9] was measured by Hypair FeNO, Medisoft.

At the subsequent visit (two to four years after removal from the exposure) the same tests were performed with the exception of the SIC.

Results

The average age of the patients was 45.8 yr; the average duration of exposure was 5.5 yr. The data characterizing the patients, latency to first symptoms, duration of exposure and outcome after removal are shown in Table 1.

Table 2 presents the results of the non-specific bronchoprovocation test, the specific bronchoprovocation and rhinoprovocation tests, as well as the time of FEV_1 decrease. A dual response was seen after the challenge test in Patient 4. Patients 1, 3 and 4 had to be tested with their corticosteroid medication because it was not possible to stop the treatment without the risk of their asthma worsening.

The results of the skin prick tests, IgE, ECP, FeNO, FEV_1 and the medication of the patients at the time of diagnosis and during the follow-up examination are shown in Table 3.

The diagnosis of occupational asthma was confirmed by bronchoprovocation tests in the SIC-exposure box in Patients 1, 3, and 4. The exposure at the workplace confirmed the diagnosis of occupational asthma in Patient 2 (after the test in the exposure box was negative). Occupational rhinitis was confirmed in Patients 2 and 5. Details of the tests are summarized in Table 3. Only Patient 5 suffered from other symptoms caused probably by exposure to $KAlF_4$ (nose bleeding and eye irritation).

Ten more subjects from the same plant in whom the diagnosis of OA and/or OR was suspected were sent to our department between 2004 and 2014. One of them was diagnosed with OR. One subject was not tested due to her pregnancy, however, work-related symptoms of asthma were present and her elimination test was positive. The occupational origin of OA was not proven by SICs in seven subjects. The testing of one subject was arranged and another one refused to be tested at the workplace. However, the total number of subjects leaving the factory suffering from the symptoms has not been recorded.

Table 2. Results of provocation tests at the time of diagnosis

Patient	Medication-1	24-h variation of FEV_1 (%)	Nonspecific provocation test	Bronchodilatation test with salbutamol	FEV_1 before specific provocation test (%)	Decrease of FEV_1 after specific provocation in exposure box (%)	Decrease of FEV_1 after specific provocation at workplace	Time of onset of significant FEV_1 decrease after provocation	Active anterior rhinomanometry	Diagnosis
1	fluticasone 100 µg	6.8	positive (histamine PC_{20} 5 mg/ml)	positive	101.3	21.9	ND	2 h after test	ND	OA
2	none	6.8	negative (histamine)	ND	110	3.5	12.4 (decrease of MEF25 30%, wheezing)	4 h after test	non-significant changes	OA
3	beclomethasone 400 µg	10.9	ND	positive	73.3	20	ND	immediately after test	Lflow –59%, Rflow –39%, Lres +244, Rres +63%	OA, OR
4	budesonide 800 µg	8.1	positive (methacholine PD_{20} 0.05 mg)	positive	95.3	30.4 and 25.5	ND	immediately after test and 8.5 h after test	non-significant changes	OA
5	none	3	negative (methacholine)	ND	106.7	3.1	ND	NA	Lflow –41%, Rflow –41%, Lres +100%, Rres +68%	OR

Medication-1: topical corticosteroids treatment taken at the time of the challenge test, daily dose, FEV_1: forced expiratory volume in 1 second, PC_{20}: the provocative concentration required to decrease FEV_1 by 20% from baseline, PD_{20}: the provocative dose required to decrease FEV_1 by 20% from baseline, Lflow: nasal flow − left side, Rflow: nasal flow − right side, Lres: nasal resistance − left side, Rres: nasal resistance − right side, OA: occupational asthma, OR: occupational rhinitis, ND: not done, NA: not applicable

Table 3. Results of parameters at the time of diagnosis (1) and at the follow-up examination (2)

Patient No/units	Skin prick tests- positivity	IgE-1 IU/ml	ECP-1 ng/ml	FeNO-1 ppb	Medication-2	FEV_1-2 %	IgE-2 IU/ml	ECP-2 ng/ml	FeNO-2 ppb
1	grass, rye, wormwood	143	71.6	ND	fluticasone (topical), salmeterol, salbutamol	100	108	29	ND
2	mites, feathers, cockroaches	ND	37	ND	ciclesonide (topical), salbutamol	88	27	36	16
3	hay	467	47.6	ND	beclomethasone (topical), formoterol, salbutamol	50	635	13	12
4	mites, grass, spring pollen	78	24	ND	methylprednisolone (oral), fluticasone (topical), salmeterol, formoterol, salbutamol, montelucast, theophylline, omalizumab, mometasone (intranasal)	70	ND	6	14
5	mould	17	46	34	montelucast, fluticasone (intranasal)	95	16	32	27

Time of diagnosis (1): IgE-1, ECP-1, FeNO-1 (for Medication 1 and FEV_1 please see Table 2). Follow-up examination (2): Medication-2, FEV_1-2, IgE-2, ECP-2, FeNO-2. IgE: immunoglobuline E, ECP: eosinophilic cationic protein, FeNO: fractional exhaled nitric oxide, FEV_1: forced expiratory volume in 1 second, ND: not done

Discussion

The case series reported here describes the full investigation of a case-series of five patients with OA and/or OR attributed to exposure to powdered $KAlF_4$ used as a flux for aluminium brazing. To our knowledge, it belongs to one of a few references regarding series of OA and/or OR due to aluminium brazing used in the production of a wide range of final products in air-conditioning, refrigeration and other applications, including the large automotive sector. In every subject, a diurnal variability has been measured and compared with the results of the SIC. The diurnal variability of PEF and FEV1 at rest (without any provocation) did not exceed 20% in any patient. Therefore, in spite of the fact that a classic control placebo challenge test has not been conducted, the evidence of causal relationship between OA and/or OR and work-relatedness in all described cases has been clear and consistent. The sensitivity and specificity of SIC is high and can be used as the reference standard for the diagnosis of occupational asthma[10]. As a consequence the OA and/or OR was judged to have been caused by work and all the described subjects were compensated according to the Czech national law.

It is important to emphasize that the real number of cases of OA/OR due to KAlF4 exposure in the mentioned factory will most likely be much higher. As documented above, other cases appeared later. In addition, some subjects refused to be tested and probably many cases were not reported at all due to fear of losing a job. In our view, these five well-characterized subjects are an underestimate of the number (and hence prevalence/incidence) of occupational asthma/rhinitis associated with $KAlF_4$ in this industry.

Asthma and fluorides in general

Potroom asthma has been described with regard to the exposure to pollutants such as AlF_3 and $NaAlF_4$ and trace elements (vanadium, chromium and nickel) during electrolytic production of aluminium from Al_2O_3. Work-related asthmatic symptoms have been associated with workplace air concentrations of fluorides in the Norwegian aluminium industry; the relative risk was 3.35 for a fluoride concentration of 0.41–0.80 mg/m^3 and 5.20 for more than 0.80 mg/m^3[3, 11].

Soyseth *et al.*[12] studied the potential association of the plasma level of fluorides with the bronchial responsiveness in 26 potroom workers with asthmatic respiratory symptoms. They have been examined using a methacholine challenge test every three months for two years, always after five to six hours of work. Each time, blood samples measuring the plasma level of fluorides were taken before these tests. Results of this study showed a positive correlation of bronchial hyperreactivity with plasma fluorides level.

In a Norwegian aluminium plant in 2000, Romundstadt *et al.*[13] showed a positive association between exposures to potroom emissions measured by fluorides and mortality following chronic obstructive lung disease (asthma, emphysema and chronic bronchitis combined) in the smelters exposed for at least three years between 1962–1996.

Asthma and $KAlF_4$

$KAlF_4$ is a well-known irritant and its producers denied its allergenic potential. Accordingly, skin tests indicated that flux containing fluorides was primarily an irritant and did not cause an allergy. The first report in the literature concerning $KAlF_4$ was written by Hjortsberg *et al.*[14] in 1986. The study was performed in a Swedish soldering plant. After a longer period of time spent in $KAlF_4$ flux exposure, workers reported symptoms of bronchial asthma and bronchial hyperreactivity. In this study, five out of seven workers exposed to $KAlF_4$ developed bronchial hyperreactivity and/or bronchial asthma. The time-weighted average concentration of respirable dust in this plant was under 1 mg/m^3, i. e. one-fifth of the valid Swedish air limits, which raised suspicion of an immunologic mechanism. Therefore, Hjortsberg *et al*. stressed the need for specific occupational/hygienic standards and for regular check-ups, including bronchial hyperreactivity tests, among the workers exposed to $KAlF_4$.

Hjortsberg *et al.*[15] also reported a study of 22 workers exposed to $KAlF_4$ in another aluminium soldering company in 1994. The employees were examined due to their showing symptoms of irritation of the eyes, skin and airways. Rather surprisingly, the median (range) latency time for the development of respiratory symptoms was long and lasted for 6 (1–60) months on average. Twenty-one out of the 22 subjects reported cough or chest tightness after exposure to the flux. All workers exposed to the flux described a slow improvement of their symptoms during a sick leave and after leaving the job. Sixteen of them volunteered for a methacholine provocation test. Hyperreactivity in small airways was found in 50% of them.

In 1999, Hjortsberg[16] suggested that $KAlF_4$ may have a non-specific modulatory function in the IgE-mediated immune response through G-protein activation.

On the other hand, Burge *et al*.[17] suggested a type of IIA, typically with a long latency, comparable to hypersensitivity OA, that developed within 4 months due to exposure to a moderate level of irritants, mostly in those subjects with childhood asthma and atopy. In this study, the authors compared 127 workers with IIA and 1,646 subjects with hypersensitivity OA from the Shield database (a voluntary reporting scheme for OA in West Midlands, UK) and found no differences in terms of pre-existing asthma, atopy, age, latent interval, non-specific reactivity and smoking. He concluded that the clinical unit of IIA is currently indistinguishable from OA due to sensitization.

We consider our case series to be consistent with the diagnosis of irritant-induced asthma with latency, as suggested by Burge *et al.*, based on their criteria:

1) Our subjects had no history of childhood asthma and were all asymptomatic when entering the job (patients 1 and 3 had a history of pollinosis only, and patient 5 of childhood dermatitis).

2) They developed symptoms of OA within 1–4 yr of latency (latency of 4 yr was seen in the 3 subjects with a history of pollinosis and dermatitis). All previous workers started to work before 2007 when the air concentrations still exceeded the borderline of the allowed workplace limit, but no accident with acute high exposure occurred.

3) The symptoms related to the usual exposure to the causative agent $KAlF_4$.

4) The symptoms were reproducible with SIC.

Prevention and vigilance

Using $KAlF_4$ flux apparently represents a new risk of developing OA and OR. To our knowledge $KAlF_4$ use particularly in air-conditioner production has not been described in the literature yet. The symptoms started in several subjects while working in a workplace that exceeded the borderline limits for fluorides; however also in the recent years, when the exposure has been much lower, further subjects have been sent to our department and there still appears to be a problem. In our opinion, subjects entering these jobs need special attention, including more intense preventive measures and personal protection related to the exposure to $KAlF_4$. In addition, they should be examined by an occupational physician more frequently. The necessity to examine all workers leaving an industry should be highlighted, as subjects quitting such jobs because of their symptoms may lower the prevalence of health problems in the workforce.

It is important to search for new causes of occupational diseases as this may speed up the process of finding the diagnosis, and act as early primary and secondary prevention. One effective method is searching through national databases[18].

Moreover it is very important to emphasize the need for cooperation at international level and to work together on searching for new and emerging occupational diseases (either not yet identified or occurring in a new occupational context). This idea has been carried out, for example, by the multinational consortium MODERNET (network for development of new techniques for discovering trends in occupational and work-related diseases and tracing new and emerging risks www.costmodernet.org), a monitoring system based on the reporting done by physicians. Such a network may support the cooperation of occupational and

safety specialists and physicians as well as enable a rapid exchange of information to take preventive actions.

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