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Occupational asthma and rhinitis in workers from a lasamide production line

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Objectives A wide range of low-molecular-weight agents can cause occupational asthma. The chemical industry is an environment in which numerous hazardous substances are used. Lasamide (2,4-dichloro-5-sulfamoylbenzoic acid) is one of them (along with its precursors).

Methods Five patients from a lasamide production line with suspected occupational asthma and rhinitis were examined. During the first visit, skin prick tests, total immunoglobulin E (IgE), a nonspecific bronchoprovocation test, and specific bronchoprovocation tests using occupational agents were performed to confirm the diagnosis of allergic diseases. During the follow-up visit (1–3 years after removal from exposure), all of the tests (except the specific bronchoprovocation test) were performed again.

Results At the first hospitalization, the total IgE levels were increased in three patients. In addition, skin prick tests and the nonspecific bronchoprovocation test were positive for three patients. After the specific bronchoprovocation test, serious bronchoconstriction occurred in three patients; symptoms of rhinitis were present in all five patients. Several years after removal from exposure to the occupational agents, normalization (with respect to the parameters followed) was not yet complete for all of the patients.

Conclusions The process of lasamide production seems to be hazardous and is likely to cause allergic respiratory disease. The prognosis of allergic diseases caused by these products is not very favorable. Allergic symptoms (despite the removal from occupational allergen exposure) persisted even after several years.

Key terms 2,4-dichloro-5-chlorsulfonylbenzoic acid; 2,4-dichloro-5-sulfamoylbenzoic acid; bronchoconstriction; furosemide; rhinomanometry; specific test.

Lasamide (2,4-dichloro-5-sulfamoylbenzoic acid) is one of the substances produced in the Synthesia chemical plant located in Pardubice-Semtín, Czech Republic. It is used in the manufacture of furosemide (4-chloro-N-furfuryl-5-sulfamoylanthranilic acid), a diuretic marketed under the brand names Lasix, Furon, Furosemid, and the like. In the first production step, 2,4-dichlorobenzoic acid reacts with chlorsulfonic acid to form 2,4-dichloro-5-sulfonylbenzoic acid. The subsequent intermediate is 2,4-dichloro-5-chlorsulfonylbenzoic acid, and then 2,4-dichloro-5-sulfamoylbenzoic acid (lasamide) is obtained. The reactions are carried out in a closed system. Lasamide is separated using a membrane filter press, and it is collected into barrels for drying on a fluidization dryer in an air-conditioned hall. Exposure to these chemicals is possible during the handling, drying, and packaging of lasamide. Twelve workers are directly

exposed to these substances during lasamide production, and 49 workers are indirectly exposed while working in the same hall but on another production line. To our knowledge, lasamide is produced only in the Czech Republic, China, and India.

Lasamide, with a molecular weight (MW) of 270.09, is a white crystalline powder. According to the Synthesia Semtín material safety data sheets (MSDS) and acute toxicity tests performed by the Centre of Ecology, Toxicology and Analytics (CETA) of the Research Institute of Organic Syntheses Ltd, it is not classified as a hazardous substance. It has a low oral and dermal toxicity in rats, with an oral LD₅₀ (50% lethal dose) of more than 12 000 mg/kg and a dermal LD₅₀ of more than 5000 mg/kg. In rabbits, it does not cause dermatitis, and it is only a mild eye irritant. According to the Synthesia Semtín MSDS and CETA, 2,4-dichlorobenzoic acid

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(MW 191.01) is an eye, skin, and respiratory irritant (oral LD₅₀ of 1280 mg/kg for rats); neither 2,4-dichloro-5-sulfonylbenzoic acid (MW 255.08) nor 2,4-dichloro-5-chlorsulfonylbenzoic acid (MW 289.52) are classified as toxic, the oral and dermal LD₅₀ being more than 2000 mg/kg for rats.

New potential low-molecular-weight allergens in the chemical industry are reported in this article; neither lasamide nor its precursors have, to date, been reported to cause allergic rhinitis and asthma.

Study population methods

Five male patients from the lasamide production line examined for possible occupational allergic diseases were diagnosed with occupational asthma and rhinitis. Their medical histories indicated possible exposure to allergens in the workplace.

During the first hospitalization, the following parameters were determined, and the following tests were performed: total immunoglobulin E (IgE), skin prick tests with environmental allergens, nonspecific bronchoprovocation tests, and specific bronchoprovocation tests with the suspected occupational allergens. Control tests with a placebo (sodium chloride) were carried out (1).

The patients did not take any antiasthmatic or anti-allergic medication while being tested. At follow-ups (1–3 years after removal from occupational allergen exposure) all of the examinations, except the specific bronchoprovocation tests, were performed again.

Skin prick tests (Sevapharma, Czech Republic) were done with common environmental respiratory allergens (dust, feathers, mites, pollen–grass, spring and autumn mixture, molds, upper respiratory tract bacteria) (2). The suspected occupational allergens were not tested.

Spirometry and body plethysmography were both performed using MasterLab and MasterScreen (Jaeger, Germany), in line with the recommendations of the European Respiratory Society (3, 4).

Nonspecific bronchoprovocation tests were first performed with acetylcholine (at concentrations of 1, 2.5, and 10 or 5 mg/ml) for two patients and later with histamine (at concentrations of 1, 5, and 10 mg/ml), using the Asthma Provocation System (APS) Jaeger (dosimeter method). A decrease in forced expiratory volume in 1 second (FEV₁) exceeding 20% of the baseline level was considered to be a positive result (5, 6).

The specific bronchoprovocation tests were performed with the compounds used in the lasamide production and suspected of causing asthma or rhinitis. Patients 1, 2, and 3 were only tested with 2,4-dichloro-5-chlorsulfonylbenzoic acid. Patient 4 was tested with lasamide (2,4-dichloro-5-sulfamoylbenzoic acid) in the form of both dried powder (final product) and raw paste (product prior to drying), 2,4-dichlorobenzoic acid, and

2,4-dichloro-5-chlorsulfonylbenzoic acid. Patient 5 was assayed with the same compounds as patient 4, with the exception of 2,4-dichlorobenzoic acid. The patients simulated their work with the aforementioned chemicals in quantities of several grams in a special exposure hood for 30 minutes. They imitated their workplace exposure during the lasamide handling, drying and packaging into barrels.

Spirometry followed immediately after the test, at 2, 5, and 24 hours after the test, and any time when the patient did not feel well. The diagnosis was set when at least one of the following three criteria was met: (i) a decrease in FEV₁ by more than 20% compared with the baseline level prior to the test (the main criterion), (ii) a decrease in the mean expiratory flow (MEF) at a 25%, 50%, or 75% of the lung volume (MEF₂₅, MEF₅₀, MEF₇₅, respectively, of the percentage of the forced vital capacity) of more than 30% when compared with the baseline level (secondary criterion), plus symptoms, (iii) an increase in the total airway resistance (R_{tot}) by more than 70% when compared with the baseline value (secondary criterion), plus symptoms. The final diagnosis of occupational asthma was determined on the basis of the results of the specific tests, medical history, and other laboratory analyses.

Occupational rhinitis was diagnosed on the basis of the rhinomanometry results, symptoms (nasal blockage, sneezing, rhinorrhea) and the disease history. Anterior rhinomanometry was performed using a Rhinoscreen (Jaeger, Germany). A flow volume reduced to less than 60% of the baseline value or nasal resistance increased by at least 60% when compared with the baseline value (7) was considered positive.

No control provocations were performed for the healthy workers.

All of the examinations and tests were approved by the Ethics Committee of the 1st Faculty of Medicine, Charles University, Prague, and all persons enrolled in this study provided their written informed consent for all of the tests.

The characteristics of the patients are summarized in table 1.

Results

Patient 1 had worked in the chemical industry for 15 years, and for 4 years mainly on the lasamide production line. His health problems started 3 years after beginning his work on the lasamide line, with sneezing, rhinorrhea, cough, and dyspnea. He was referred to our department 1 year after the onset of his problems.

At the time of diagnosis, he tested positive for total IgE (negative in the follow-ups), negative in the skin prick test (remained negative at the follow-ups), and negative in the nonspecific bronchoprovocation test

Table 1. Characteristics of the examined patients at the time of diagnosis (first visit in our department). (FEV₁% = forced expiratory volume in 1 second—percentage of predicted forced expiratory volume in 1 second, FVC = forced vital capacity)

Pa-tient	Age (years)	Smoking	Total duration of exposure (years)	Latency period (years)	Atopy (skin prick tests)	Non-specific bronchial hyperre-activity	Baseline FEV ₁ (%)	Baseline FEV ₁ /FVC
1	54	Ex-smoker	4	3	No	No	118.0	82.6
2	57	Ex-smoker	4	2.5	No	Yes	95.7	82.0
3	46	Ex-smoker	5.5	2–3	Yes	Yes	87.8	81.6
4	30	Nonsmoker	5.5	4–5	Yes	Yes	84.6	84.0
5	30	Ex-smoker	5.5	2–3	Yes	Not done	91.7	78.4

(positive only at follow-up 1). The specific bronchoprovocation test with 2,4-dichloro-5-chlorosulfonylbenzoic acid appeared positive (FEV₁ decreased to 70% of the baseline value and nasal flow as low as 11.5% of the baseline).

Patient 2 had worked in the chemical industry for 32 years, and for 4 years mainly on the lasamide production line. Sneezing and rhinorrhea started 2.5 years after he began work with lasamide and its precursors, with dyspnea and wheezing observed half a year later. He was screened for occupational disease 1.5 years after the onset of his problems.

The total IgE and skin prick tests were and remained negative at both the time of diagnosis and in the follow-ups; the nonspecific bronchoprovocation test was positive at the time of diagnosis and at follow-up 2. The specific bronchoprovocation test with 2,4-dichloro-5-chlorosulfonylbenzoic acid was borderline (FEV₁ decreased to 89% of the baseline, R_{tot} rose to 194.1% of the baseline level, and nasal flow fell to 28.5% of the baseline level). The diagnosis of asthma was given with caution for this patient, who only met the positivity criterion for R_{tot} while his positivity in the test was not clear.

Patient 3 had worked in the chemical industry for 5.5 years, mainly on the lasamide line. His health problems started after 2–3 years, with sneezing and rhinorrhea, followed by dyspnea, wheezing and cough. Three years later, he was referred to our department for diagnosis.

The patient tested positive in the specific bronchoprovocation test with 2,4-dichloro-5-chlorosulfonylbenzoic acid; his FEV₁ decreased immediately to 53.0% of the baseline level to fall further to 74.3% of the baseline level 5 hours after exposure. His nasal flow increased to 232.0% of the baseline level. On the basis of his symptoms (ie, intermittent nasal blockage, sneezing and rhinorrhea), he was also diagnosed with occupational rhinitis. Total IgE and the nonspecific bronchoprovocation test were positive both at the time of the diagnosis

and at the follow-ups; the skin prick tests were positive only at the time of diagnosis and at follow-up 1.

Patient 4 had worked in the chemical industry for 9 years, and for 5.5 years mainly on the lasamide production line. Rhinorrhea, nasal blockage, and conjunctivitis developed after 4–5 years, followed by dyspnea and cough half a year later. Because of these persisting health problems, the patient was removed from the workplace.

The patient tested positive in the skin prick tests and IgE negative both at the time of the diagnosis and in the follow-ups, but showed positivity in the nonspecific bronchoprovocation test at the time of the diagnosis only. Although the specific bronchoprovocation tests with lasamide, 2,4-dichloro-5-chlorosulfonylbenzoic acid, and 2,4-dichlorobenzoic acid were negative, we observed reduced nasal flow (to 30.4%, 16.9% and 18.1% of the baseline level, respectively) and symptoms of rhinitis.

Patient 5 had worked in the chemical industry for 10 years, and for 5 years mainly on the lasamide production line. Conjunctivitis, rhinorrhea, cough, and dyspnea started after 2–3 years. He was examined in our department 2 years after the onset of his problems.

Total IgE and skin prick tests were positive both at the time of the diagnosis and in the follow-ups; the nonspecific bronchoprovocation test was negative in the follow-up (not performed at the time of diagnosis). The specific bronchoprovocation tests with 2,4-dichloro-5-chlorosulfonylbenzoic acid and lasamide were negative. The patient manifested symptoms of rhinitis, and his nasal flow was reduced to 28.4% of the baseline level in the test with 2,4-dichloro-5-chlorosulfonylbenzoic acid.

In conclusion, three out of the five screened patients were diagnosed with occupational asthma, and all of the five patients suffered from occupational rhinitis. All of the patients tested negative in the control tests with sodium chloride (ie, none of them showed a decrease in FEV₁ by more than 20% when compared with the baseline level).

The results of the specific bronchoprovocation tests are summarized in table 2.

Discussion

In industrialized countries, both occupational asthma and rhinitis are among the most prevalent occupational respiratory diseases. To identify occupational allergens and to control workplace exposure are priorities for occupational safety. Controlled laboratory exposure to allergens provides the possibility for diagnosing occupational asthma. Exposure to specific asthmagens is considered the gold standard for the diagnosis of occupational asthma (8–10). In most countries, specific

Table 2. Results of the specific bronchoprovocation tests. (FEV₁ = flow expiratory volume in 1 second, OA = occupational asthma, OR = occupational rhinitis)

Pa-tient	Tested allergen	FEV ₁ before test (l)	FEV ₁ after test (l)	FEV ₁ 2 h after test (l)	FEV ₁ 5 h after test (l)	Maximum decrease in FEV ₁ after test (%)	Total airway resistance ^a (%)	Maximum change in total nasal flow after test (%)	Symptoms during test	Result of test (reason)
1	2,4-Dichloro-5-chlorsulfonylbenzoic acid	4.60	3.20	4.96 ^b	4.76	-30.0	+359.0	-88.5	Dyspnea, wheezing, nasal blockage, sneezing, rhinorrhea	Positive occupational asthma + occupational rhinitis (significant decrease of FEV ₁ and nasal flow, symptoms)
2	2,4-Dichloro-5-chlorsulfonylbenzoic acid	3.48	3.08	3.28	3.32	-11.0	+94.1	-71.5	Dyspnea, cough, nasal blockage, rhinorrhea	Positive occupational asthma + occupational rhinitis (significant increase in total respiratory resistance plus symptoms, significant decrease in nasal flow plus symptoms of rhinitis)
3	2,4-Dichloro-5-sulfonylbenzoic acid	3.33	1.76	2.97 ^b	2.47	-47.0 after 5 h: -25.7	+219.6, after 5 h: +82.8	+232.0	Dyspnea, cough, intermittent nasal blockage, sneezing, rhinorrhea	Positive occupational asthma + occupational rhinitis (significant decrease in FEV ₁ , serious symptoms of rhinitis)
4	Lasamide (dried powder and raw paste)	3.39	3.07	3.17	3.28	-9.5	+4.8	-69.6	Rhinorrhea, nasal obstruction, sneezing, cough	Positive occupational rhinitis (significant decrease in nasal flow plus serious symptoms of rhinitis)
4	Lasamide (dried powder)	3.39	3.15	3.31	3.21	-7.3	-1.1	-14.1	Rhinorrhea, nasal blockage, sneezing, cough, dyspnea	Negative
4	Lasamide (raw paste)	3.45	3.17	3.16	3.17	-8.4	+17.2	-19.3	Mild rhinorrhea, cough	Negative
4	2,4-Dichloro-5-chlorsulfonylbenzoic acid	3.27	3.04	3.32	3.13	-7.1	-7.8	-83.1	Rhinorrhea, nasal blockage, cough	Positive occupational rhinitis (significant decrease in nasal flow plus serious symptoms of rhinitis)
4	2,4-Dichloro-benzoic acid	3.06	2.94	2.97	2.96	-4.0	+6.0	-81.9	Nasal blockage, rhinorrhea, cough	Positive occupational rhinitis (significant decrease in nasal flow plus serious symptoms of rhinitis)
5	Lasamide (dried)	4.64	4.80	4.76	4.64	0	+16.0	-31.7	Nasal blockage, rhinorrhea, cough	Negative
5	Lasamide (raw)	4.60	4.44	4.64	4.56	-3.5	+58.9	-35.6	Nasal blockage, rhinorrhea, cough	Negative
5	Lasamide (dried, raw)	4.60	4.40	4.68	4.64	-4.3	+18.8	-12.4	Nasal blockage, rhinorrhea	Negative
5	2,4-Dichloro-5-chlorsulfonylbenzoic acid	4.52	4.28	4.48	4.44	-5.3	+18.0	-71.6	Dyspnea, cough, nasal blockage, sneezing, rhinorrhea	Positive occupational rhinitis (significant decrease in nasal flow plus serious symptoms of rhinitis)

^a Secondary criterion.^b The value after the application of a short-acting β_2 agonist.

challenge tests are not commonly used because of the difficulty of implementing them, since the patient needs to be hospitalized. Serial measurements of peak expiratory flow (PEF) rates are used instead; they require, however, the close cooperation of the patient.

Lasamide is an intermediate used in the manufacture of the diuretic furosemide, and both agents are characterized by the presence of SO₂NH₂ moiety in their structure. An American study did not reveal a higher risk of allergic reaction to nonantibiotic sulfa drugs for patients with allergy to sulfonamide antibiotics than in those allergic to other nonsulfonamide drugs (11). In a review article, Johnson et al (12) found only one case report on the cross-reactivity between furosemide and sulfonamide drugs.

Jarvis et al (13) focused on the relationship between the chemical structure of various compounds and the

risk of developing asthma. Both lasamide and 2,4-dichloro-5-chlorsulfonylbenzoic acid contain several substructure fragments (aromatic to sulfur, carboxylic acid, sulfur, amine, aromatic to carbonyl, benzyl, carbonyl) whose hazard odds ratios for developing asthma were calculated. Their findings support the asthmagenic or allergenic potential of the two chemicals in our study.

In conclusion, the process of lasamide production is likely to pose a health risk because of the use of potential allergens or asthmagens. The allergic symptoms did not resolve for any of our patients after removal from occupational allergen exposure, and four of the five patients received medication to control their diseases. Lasamide and its precursors are new allergens, and the early removal of the patient, with the first respiratory symptoms, from occupational exposure is essential for restoring quality of life.

The reported cases indicate that lasamide and 2,4-dichloro-5-chlorosulfonylbenzoic acid may cause occupational asthma and rhinitis.

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