

Case report

Occupational rhinitis and bronchial asthma due to morphine: evidence from inhalational and nasal challenges

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A case of occupational bronchial asthma due to morphine in a nonatopic 46-year-old woman is presented. The following diagnostic tests were used: a workplace trial with bronchodilator and placebo, and single-blind, placebo-controlled nasal and bronchial challenge with 0.5% morphine HCl. For the nasal challenge, four asthmatic patients were selected as a control group. The nasal washings were done before and 30 min, 3 h, 24 h, and 48 h after all challenges. In the nasal lavage fluid, the total numbers of eosinophils, neutrophils, basophils, and mast cells were counted, and, after the nasal challenge, total protein and albumin levels were measured. During the workplace trial, the PEF variability ratio increased from 5% to 38%. After the challenges, a decrease in the spirometric parameters (VC and FEV₁) of about 30–40% was observed, with minimums at 24 and 48 h. An influx of granulocytes with an increase in the relative number of eosinophils and basophils from 3 h until 48 h after the challenge was observed in the nasal lavage fluid. The protein level in the nasal lavage fluid increased from 190 to 1275 µg/ml 24 h after the challenge with an increase of relative albumin level from 24% to 40% at 24 h. In the control group, no changes in relative number of basophils and eosinophils and albumin/total protein ratio in the nasal lavage fluid or in the spirometric parameters were observed after the challenge.

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Occupational hypersensitivity to opiates has been reported in few publications (1, 2). Neither the mechanisms nor the clinical symptoms of this kind of hypersensitivity have been fully described so far, and the data on specific inhalational or nasal challenges are lacking.

Contact dermatitis (3) and the presence of IgG (4) and IgM (5) class antibodies have been reported in pharmaceutical industry workers and drug users. A decrease in the spirometric parameters in pharmaceutical industry workers has also been described (1). We present a case of occupational hypersensitivity to morphine in the form of delayed respiratory tract reaction.

Case history

A 46-year-old woman had been working at a pharmaceutical plant as a drug packer, in direct

contact with powdered morphine HCl (from 1967 to 1973 and from 1991 to 1993) 5–6 h per shift. On admission to our department, she complained of paroxysmal dyspnea, wheezing, nonproductive cough, sneezing, rhinorrhea, and lacrimation. The first symptoms appeared in 1970 and comprised paroxysmal nonproductive cough, sneezing, and rhinorrhea several times during a shift. She reported her first dyspnea attack in 1970 at the workplace. From 1972 to 1973, she used to receive treatment in the outpatient department because of asthma exacerbation. After 1973, when she moved to another workplace and no longer had contact with morphine, she had a medical checkup once a year only. There was no reason for continuous treatment with antihistamines. She started to work again in direct contact with morphine in 1991, and her asthma then became exacerbated. In March 1993, occupational exposure to mor-

phine was discontinued; afterward, no asthmatic symptoms were observed. She was treated with inhaled fenoterol, beclomethasone dipropionate, and disodium cromoglycate from 1991 to 1993. During asthma exacerbation, she used to be treated with prednisone and, for 2 months, with ketotifen. The treatment with disodium cromoglycate and beclomethasone appeared to be very effective.

She had never suffered from any other allergic disease. The family history was negative.

Examinations

The following tests were performed: spirometry, the bronchial reversibility test with inhaled salbutamol, bronchial challenge with histamine, skin prick tests with common allergens, and total serum IgE level measurement. Then, the inhalational test with bronchodilator and placebo was performed at her workplace, and the bronchial reversibility test with salbutamol and nasal and bronchial challenges with morphine HCl were performed under clinical conditions.

Inhalational workplace trial with bronchodilator and placebo. The patient had to measure PEF at 1-h intervals (with a break for sleep) for 6 days of work in contact with morphine HCl (8 h daily, from 6 a.m. to 3 p.m.). She inhaled salbutamol or placebo according to the following schedule: 1st and 4th days, no treatment; 2nd and 5th days, two inhalations of placebo before her shift and two inhalations of placebo after 4 h of work; 3rd and 6th days, two inhalations of salbutamol before the shift and two inhalations of salbutamol after 4 h of work. The patient was not informed of the kind of drug used.

Inhalational challenge with morphine HCl. The challenge was performed with 0.5% morphine HCl solution in 0.9% saline inhaled through the mouthpiece of the De Vilbiss 646 nebulizer for 5 min at a flow of 0.15 ml/min. Spirometric parameters were measured before and during 48 h after the challenge, as shown in Table 1. At the same time, the patient was performing PEF measurements (with the break for sleep).

Nasal lavage procedure. Nasal lavages were performed before and 30 min, 3 h, 24 h, and 48 h after the challenge. The "nasal pool" technique was used, as described by Greiff et al. (6). A syringe closely fitting one nostril was inserted into the nasal cavity to fill it with 6 ml of 0.9% NaCl for 5 min. Then, lavage fluid was recovered and centrifuged at room temperature for 10 min at 400 g. The sediment was washed twice with sterile PBS and

then suspended in 1 ml of RPMI. The total number of eosinophils, neutrophils, and metachromatic cells (basophils and mast cells) was counted in the Fuchs-Rosenthal chamber after staining by Hansel's method. Total protein and albumin concentrations in supernatant were measured before and after the challenge with morphine and placebo.

Nasal challenge with morphine HCl. The challenge was performed by filling the nasal cavity with 6 ml of 0.5% morphine HCl in 0.9% saline for 5 min. Nasal washings were performed before and 30 min, 3 h, 24 h, and 48 h after the challenge. Selected spirometric parameters (VC, FEV₁, and PEF) were also measured within 48 h after the challenge.

Control group. Four patients with bronchial asthma and rhinitis (two women and two men aged 36–48 years) were selected for nasal challenge with morphine HCl.

Results

The examination in our department, carried out 17 months after the patient's last occupational exposure to morphine, revealed no physical changes. Basic biochemical results were within normal ranges. There were no deviations in spirometric parameters. The bronchial reversibility test with inhaled salbutamol was negative, but inhalational challenge with histamine was positive (PC₂₀ = 2.58 mg/ml, normal value = 16 mg/ml) and revealed moderate bronchial hyperreactivity. The total serum IgE concentration was 29.15 kU IgE/l. Skin prick tests with common allergens were negative. There were no abnormalities in the chest radiograph.

Inhalational workplace trial with bronchodilator and placebo

Six days' observation of PEF without exposure to morphine revealed only a 5% PEF variability ratio ($[(PEF_{\max} - PEF_{\min})/PEF_{\max}]$ observed for 24 h). During the next 6 days, when the patient was occupationally exposed to morphine HCl, the PEF variability ratio increased to 38% at day 4 (PEF_{max} = 450 l/min, PEF_{min} = 280 l/min), and the patient complained of nonproductive cough, dyspnea, wheezing, sneezing, and rhinorrhea. It should be noted that, in addition to the bronchodilator taken according to the protocol described above, the patient had to use inhaled salbutamol from the 2nd day of work (PEF values are shown in Fig. 1).

After the trial, the bronchial reversibility test with inhaled salbutamol was positive.

Table 1. Changes in spirometric parameters before and after nasal and bronchial challenges with 0.5% solutions of morphine HCl in 0.9% NaCl and with placebo (0.9% NaCl) in patient under study

	Time after challenge											
	Before		5 min after		30 min after		3 h after		24 h after		48 h after	
	VC	FEV ₁	VC	FEV ₁	VC	FEV ₁	VC	FEV ₁	VC	FEV ₁	VC	FEV ₁ [1]
Placebo, bronchial	3.34	2.20	3.31	2.18	3.36	2.28	3.26	2.17	3.41	2.24	3.39	2.19
Morphine, bronchial	3.25	2.21	3.19	2.14	3.33	2.27	3.16	2.18	2.34	1.35	2.41	1.40
Placebo, nasal	3.19	2.23	3.10	2.16	3.31	2.24	3.22	2.18	3.18	2.19	3.36	2.24
Morphine, nasal	3.31	2.18	3.30	2.18	3.24	2.10	3.11	2.01	1.92	1.18	1.98	1.21

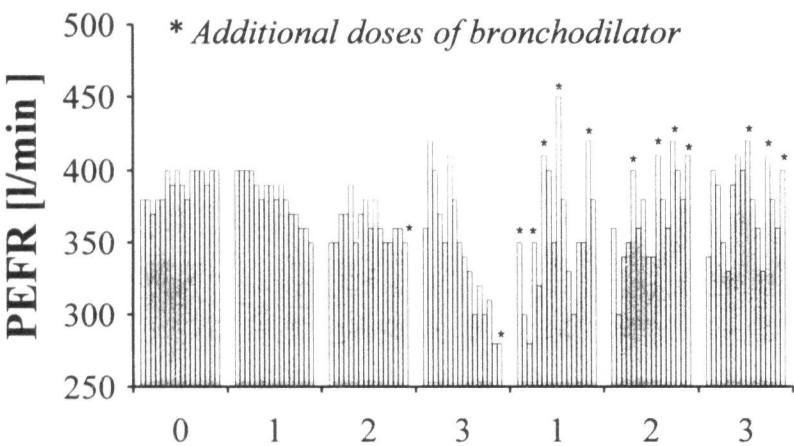


Fig. 1. Workplace trial with bronchodilator and placebo (PEF measured every hour from 6 a.m. to 9 p.m., work shift from 6 a.m. to 3 p.m.). 0 – at home; 1 – at work without drugs; 2 – at work with placebo; 3 – at work with salbutamol.

Inhalational challenge with morphine HCl

No changes in VC and FEV₁ were observed during the first 3 h after the challenge. By 24 h after, VC and FEV₁ had significantly decreased (28% and 39%, respectively), and the patient complained of dyspnea, wheezing, and rhinorrhea. Such changes were also recorded in 48 h after the bronchial challenge; the patient was not given any bronchodilator therapy during this period. Nasal lavages were performed simultaneously with the spirometric examinations to estimate the intensity of rhinitis, the degree of granulocyte influx being used as a parameter. Increased influx of granulocytes was observed 24 h after the challenge with the peak point at 48 h. An increased number of basophils was observed 3 h after the challenge. An increased number of eosinophils was also observed 3 h after the challenge with the peak point at 48 h. Changes in the nasal lavage fluid corresponded to the changes in lung ventilation.

Nasal challenge with morphine HCl

VC and FEV₁ decreased maximally 24 and 48 h after the challenge (42% and 46%, respectively, at

24 h). The patient complained of dyspnea, wheezing, sneezing, and rhinorrhea. No changes in the spirometric parameters during the first 3 h were observed.

The total protein level in the nasal lavage fluid before the challenge was 190 µg/ml, and it increased to 1275 µg/ml 30 min after the challenge, to 725 µg/ml 3 h after, to 1275 µg/ml 24 h after, and to 1120 µg/ml 48 h after the challenge. The albumin level increased from 46 µg/ml before the challenge (24.6% of total protein) to 150 µg/ml (11.76%) at 30 min, to 290 µg/ml (42%) at 3 h, to 520 µg/ml (40.7%) at 24 h, and to 510 µg/ml (40.8%) at 48 h.

An increased number of granulocytes, eosinophils, and basophils was observed in the nasal lavage fluid 3 h after challenge, with the peak point at 24 h after challenge (in spite of the decrease in total number of cells) (Table 2).

The patient did not complain of any abnormal symptoms, except dyspnea and rhinitis, after either the inhalational or nasal challenge, nor were changes in blood leukocyte count and body temperature observed.

No spirometric changes were found in the control group after the nasal challenge. An influx of granulocytes in the nasal lavage fluid, lasting for 3 h after the challenge, was observed, but there were no changes in either the relative number of basophils and eosinophils or the albumin/total protein ratio.

Nasal and bronchial challenges with placebo

No significant changes in the spirometric parameters were observed after the challenges with placebo. Neither cellular influx in the nasal lavage fluid nor increased level of total protein and albumin could be found.

Discussion

Several case reports of asthmatic reactions both in pharmaceutical industry workers working in direct

Table 2. Total number of cells and relative number of eosinophils (Eo) and metachromatic cells (Meta) in nasal lavage fluid before and after nasal and bronchial challenges with 0.5% solutions of morphine HCl in 0.9% NaCl and placebo (0.9% NaCl) in patient and in control group

	Before			30 min after			3 h after			24 h after			48 h after		
	Cells ($\times 10^3$)	Eo (%)	Meta (%)	Cells ($\times 10^3$)	Eo (%)	Meta (%)	Cells ($\times 10^3$)	Eo (%)	Meta (%)	Cells ($\times 10^3$)	Eo (%)	Meta (%)	Cells ($\times 10^3$)	Eo (%)	Meta (%)
Bronchial placebo															
Patient	24.31	1	1	21.11	2	2	29.46	2	1	36.18	1	1	18.14	1	1
Bronchial morphine															
Patient	29.55	2	1	54.51	3	1	46.9	5	2	115.81	7	2	187.8	10	2
Nasal placebo															
Patient	17.18	2	2	15.61	2	1	19.44	2	1	14.21	1	1	24.16	2	1
Control	10.11	1	1	14.8	1	1	23.32	1	1	17.21	2	1	16.23	1	0
Nasal morphine															
Patient	12.52	1	1	25.04	4	1	175.28	16	1	53.21	52	3	64.43	41	2
Control	9.23	1	1	52.8	2	1	47.34	1	1	18.39	2	1	17.56	0.5	1

contact with opiates, and in morphine and heroin abusers have been reported (1, 2). However, little is known of their immunologic character. One can assume that mastocytes, pharmacologically stimulated by opiates, play a major role, at least in some aspects of these reactions. It is possible that mast-cell degranulation by opiates is induced by the stimulation of opioid receptors.

Biagini et al. (1) observed a decrease in the spirometric parameters in pharmaceutical industry workers during 1 week of work, with the minimum values on Mondays and the return to normal values at the end of the week. This situation can be explained by the exhaustion of mediators from mast cells due to their continuous stimulation with opiates.

Considering the causes of changes in lung ventilation, one cannot forget the role of opioid receptors in the brainstem. Their stimulation has a depressive effect on the respiratory system, as manifested by a fall in the spirometric parameters (7).

However, in the case described above, the stimulation of receptors both in the mast cells and in the central nervous system cannot be the only explanation.

The nasal challenge method, along with the estimation of cell number and biochemical examination of the supernatant, allows one to distinguish between the allergic and irritant effect of various substances on the respiratory system. The increase in the number of granulocytes and total protein level in the nasal lavage fluid can be observed in the case of the irritant-type reaction (8). It is, however, brief and does not affect the relative number of eosinophils and basophils (9) or the relative concentration of albumin (10), as could be observed in the control group after the nasal challenge with morphine HCl.

In the case described above, there was an increase in the number of granulocytes, accompanied by an increase in the number of eosinophils and basophils, which lasted for 48 h. Such a response cannot be explained by a direct degranulation of mastocytes in the nasal mucosa since, in that case, one would expect an extinction of the reaction immediately after the challenge or 3–6 h later.

We may also exclude hypersensitivity-related pneumonitis because there were no physical symptoms or changes in blood granulocyte count and body temperature.

Irritant factors such as tobacco smoke, sulfur dioxide, and formaldehyde can produce axonal reflexes in the sensory fibers of the trigeminal nerve, accompanied by secretion of substance P, CGRP (calcium-gene-related peptide), and GRP (gastrin-related peptide), effects which cause increased permeability and relaxation of the smooth muscle of blood vessels and activation of the inflammatory cells (11). However, the reaction caused by neuropeptides develops much more rapidly than that observed in the patient under study. The increase of albumin level and the number of basophils and eosinophils (both relative and total) after the nasal challenge with morphine is characteristic of the inflammatory reaction.

The analysis of spirometric changes and composition of nasal lavage fluid, in view of all the above considerations, suggests the specific type of reaction.

The possibility of immunologic reactions due to the contact with opiates, in both man (12) and animals (13), was postulated in the early 1970s. The presence of specific antibodies of IgG (4) and IgM (5) classes in pharmaceutical industry workers and drug users has been reported recently. Moreover, some cases of delayed reactions from contact with

opiates have been described. They were characterized by contact dermatitis (3). No reaction of this kind has been reported in the respiratory system.

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