

Isolated late asthmatic reaction due to nickel sulphate without antibodies to nickel

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Summary

A worker with occupational exposure to nickel developed asthma a few months after starting work. Skin prick tests to nickel sulphate were negative. Inhalation challenge with nickel sulphate, at a concentration of 10 mg/ml for 30 min induced a late asthmatic reaction, starting 3 hr after the end of exposure leading to severe nocturnal attack. Tests for antibodies with nickel reactivity were negative.

Introduction

Case reports of occupational asthma due to nickel sulphate (NiSO_4) have been published (McConnell *et al.*, 1973; Malo *et al.*, 1982; Block & Yeung, 1982; Novey, Habib & Wells, 1983). Although McConnell and co-workers (1973) described a temporal pattern of asthmatic reaction which was different from the typical immediate and late reactions (Pepys & Hutchcroft, 1975), subsequent investigators identified a typical immediate (Malo *et al.*, 1982; Block & Yeung, 1982) or dual (immediate and late) reaction (Novey *et al.*, 1983). Nickel-reactive antibodies have been identified (McConnell *et al.*, 1973; Malo *et al.*, 1982; Novey *et al.*, 1983) with immediate skin reactivity to NiSO_4 (Malo *et al.*, 1982; Block & Yeung, 1982).

We describe here a subject who developed an isolated late asthmatic reaction after inhalation of NiSO_4 with no skin reaction and detectable nickel-reactive antibodies.

Case history

The subject was a 28-year-old man who started employment in a nickel and chromium electroplating industry 3 years earlier. A few months after starting work, he noticed dyspnoea, wheezing and cough. These symptoms usually appeared 5-6 hr after beginning work and were more evident in the evening and night following a day spent

at work. His symptomatology was improved on weekends. He was first seen after a period of 1.5 months away from work. At that time, his only complaint was dyspnoea on exercise and he used inhaled β_2 adrenergic agent only if needed. He had never had rhinitis or urticaria before.

Investigations

Skin tests

Skin prick tests were done with a routine battery of fifteen common inhaled allergens, as well as with NiSO_4 at 0.1, 1.0 and 10 mg/ml; there was no immediate (10-20 min) weal or flare.

Spirometry and inhalation challenges

Initial baseline FEV_1 /forced vital capacity (FVC) was 3.10 ± 0.42 l (70.1%) (predicted ratio of 86.2% according to the data by Knudson *et al.*, 1976). Histamine inhalation challenges with the Wright's nebulizer according to a standardized procedure (Cockcroft *et al.*, 1977) were carried out. The provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}) was 0.55 mg/ml, thus showing a significantly increased airway excitability (Cockcroft *et al.*, 1977; Malo *et al.*, 1983).

The results of specific inhalation challenges are shown in Fig. 1. On the control day, phosphate-buffered saline (PBS) was nebulized with the Wright's nebulizer for three consecutive periods of 10 min. There was a transient 18% fall in FEV_1 with no significant change in FEV_1 thereafter. On a different day, NiSO_4 diluted in PBS at a 10

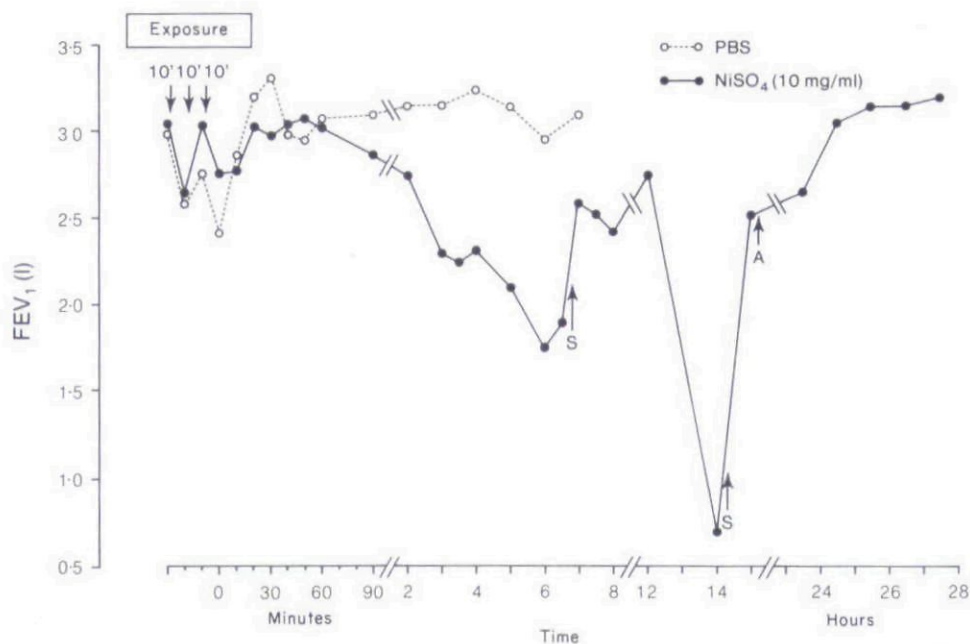


Fig. 1. Changes in FEV_1 in relation to time after exposure to phosphate-buffered saline (PBS) and nickel sulphate (NiSO_4) at a concentration of 10 mg/ml. Exposure consisted of three consecutive periods of 10 min for PBS and NiSO_4 . S = 200 μg of inhaled salbutamol given with a metered-dose inhaler; A = aminophylline (bolus of 375 mg intravenous followed by a continuous infusion of 1 g in 24 hr).

Table 1. Results of IgE and serum binding of ^{63}Ni

Source of serum	Total IgE (IU/l)	NiSO ₄ -HSA RAST (cpm)	NiSO ₄ -resin RAST (cpm)	Co-precipitated ^{63}Ni (cpm)
Subject	173	238	190	184
IgE matched controls* (mean $\pm$ s.d.)	289 $\pm$ 154	307 $\pm$ 78	209 $\pm$ 26	186 $\pm$ 16
Non-allergic controls ($n=5$) (mean $\pm$ s.d.)	ND	132 $\pm$ 8	220 $\pm$ 74	146 $\pm$ 6
Positive control†	430	737	167	421

* Obtained from three and four non-allergic individuals in the case of NiSO₄-HSA RAST and for the other tests, respectively.

† See Malo *et al* (1982).

ND: Not done.

mg/ml concentration was nebulized. There was a significant (27%) fall in FEV₁ 3 hr after the challenge which increased up to 6 hr after the end of exposure. Salbutamol given at a 200 μg concentration with the standard metered inhaler then improved significantly the FEV₁. However, the subject experienced a severe asthmatic reaction 2 hr after going to sleep. This asthma attack was relieved by the use of salbutamol and aminophylline. One month following this challenge, at a time when the baseline FEV₁ was within 6% of the first histamine challenge day, PC₂₀ had dropped to 0.043 mg/ml.

Immunological study

Measurements of total IgE was by the Phadebas method (Pharmacia Ltd, Dorval, Canada). Measurement of specific IgE antibodies was by a modification of the test described by Cromwell *et al.* (1979) as fully described elsewhere (Malo *et al.*, 1982). Also, specific IgE antibodies were tested by the method recently proposed by Novey and co-workers (Novey *et al.*, 1983). In this method, NiSO₄ is linked with resin instead of the usual binding to human serum albumin (HSA). The presence of nickel-reactive antibodies was also tested by the ammonium sulphate co-precipitation test with ^{63}Ni as detailed elsewhere (Malo *et al.*, 1982). Results of these tests are listed in Table 1. The values observed in our subject for specific IgE antibodies and co-precipitated ^{63}Ni were not significantly different from those obtained in IgE-matched controls and in non-allergic individuals. Results of specific IgE antibodies as assessed by binding to human serum albumin but not to resin as well as co-precipitated ^{63}Ni were significantly higher in a positive control subject with occupational asthma to nickel sulphate who was previously described (Malo *et al.*, 1982).

Discussion

Asthmatic reactions caused by metals such as platinum (Cromwell *et al.*, 1979), chromium (Novey *et al.*, 1983) and nickel (McConnell *et al.*, 1973; Malo *et al.*, 1982; Block & Yeung, 1982; Novey *et al.*, 1983) are now well recognized. Our subject illustrates that nickel can cause an isolated late asthmatic reaction. In previous reports, immediate (Malo *et al.*, 1982; Block & Yeung, 1982) and dual (Novey *et al.*, 1983)

asthmatic reactions had been described. An irritant mechanism can reasonably be excluded on the following evidence. Firstly, the reaction was non-immediate. Secondly, there was a very significant (> 10 -fold) change in PC_{20} and such changes have been described in late asthmatic reactions due to antigenic exposure (Cartier *et al.*, 1982; Malo *et al.*, 1983). Thirdly, a control asthmatic subject with a similar bronchial responsiveness to histamine ($PC_{20}=0.40$ mg/ml) did not react to inhaled $NiSO_4$ (Malo *et al.*, 1982).

The exact mechanism of the late asthmatic reaction caused by $NiSO_4$ in this specific example is unclear as no nickel-reactive antibodies were detectable in tests for IgE antibodies or labelled antigen binding. In the present report, we used two different techniques for measurement of specific IgE antibodies to $NiSO_4$. One of these techniques was recently proposed by Novey *et al.* (1983). According to these authors, this method offers better discrimination between positive and negative sera than the usual method using HSA as a binding ligand. However, the fact that results with this recently proposed method were in the normal range with the serum of positive control individuals with $NiSO_4$ -induced asthma with known nickel-reactive IgE antibodies raises doubts about the sensitivity of this method. Finally, in addition to antigenic stimuli, it is now known that other factors, such as exercise, can stimulate late asthmatic reactions (Nagy, Lee & Kay, 1982; Lee *et al.*, 1983). Thus, there is a possibility that $NiSO_4$ can elicitate asthmatic reaction through a non-antigenic mechanism.

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