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Cobalt-induced Occupational Asthma associated with Systemic Illness

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We report a case of occupational asthma caused by cobalt associated with systemic symptoms. He was a non-atopic, ex-smoker and had worked in a glassware factory for 14 months. A skin prick test with $CoSO_4$ up to 100 mg / ml showed a negative result. A bronchoprovocation test with $CoSO_4$ demonstrated an isolated asthmatic response with systemic symptoms such as fever, arthralgia and myalgia. Although an initial methacholine bronchial challenge test showed a negative result, the following methacholine bronchial challenge test which was done 24 hours after the challenge testing demonstrated an increased airway hyperresponsiveness at 2.5 mg / ml which recovered 7 days later. An intradermal skin test with 10 mg / ml and 100 mg / ml $CoSO_4$ solution demonstrated positive responses respectively(13 ×12 / 40×32, 20×15 / 40×37 ⟨mm⟩, histamine 16×14 / 64×50). A patch test including cobalt showed a negative result. Bronchoalveolar lavage fluid after the cobalt inhalation testing and other laboratory findings showed no evidence of hypersensitivity pneumonitis.
These results suggested that cobalt could induce occupational asthma with systemic illness in an exposed worker.

Key Words : *Cobalt, Occupational Asthma, Systemic illness*

INTRODUCTION

Many investigators have reported occupational asthma from metals such as nickel(Block and Yeung, 1982 ; Davies, 1986), chromium(Novey et al., 1983 ; Park et al., 1994), zinc(Malo and Cartier, 1987), aluminium(Hjortsberg et al., 1986) and cobalt(Bruckner, 1967 ; Davison et al., 1983 ; Gheysens et al., 1986 ; Kusaka et al., 1990 ; Shirakawa et al., 1992 ; Cugell, 1992 ; Swennen et al., 1993). Cobalt is commonly used in glass-ware making factories, radiation therapy and as a hard metal, an alloy of tungsten carbide in a matrix of cobalt to which small amounts of titanium, nickel, chromium, niobium, vanadium, or tantalium may be added.

Exposure to cobalt via inhalation has induced asthmatic reactions(Bruckner, 1967 ; Davision et al., 1983 ; Gheysens et al., 1986 ; Van Custem, 1987 ; Shirakawa et al., 1992 ; Kusaka et al., 1990 ; Cugell, 1992 ; Swennen et al., 1993), hypersensitivity lung disease(Sjogren et al., 1980 ; Davison et al., 1983) and interstitial pulmonary fibrosis(Davison et al., 1983 ; Demedts, 1984 ; Van Custem, 1987 ; Cugell, 1992). Since the first case of occupational asthma with hard

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metal exposure was reported in 1967(Bruckner), they have been reported in diamond polishers(Gheysens et al., 1986 ; Van Custem, 1987) and workers exposed to hard metal dust(Shirakawa et al., 1992 ; Kusaka et al., 1990 ; Cugell, 1992 ; Swennen et al., 1993). We report a case of occupational asthma due to cobalt associated with systemic symptoms in a glass-ware making factory worker.

CASE SUMMARY

The patient was a 48-year old ex-smoker male, who was admitted to the Allergy Clinic of the National Medical Center, Seoul, in April 1993. Fourteen months earlier, he had been employed at a glass-ware factory and his job included mixing glass powder to color glass ware in which cobalt was used as powder. He had handled cobalt, abietic acid, $NaHCO_3$ and manganese together. He had begun to experience cough and shortness of breath four months before the study and had suffered from rhinorrhea, sneezing, febrile sensation and generalized weakness in the previous two months. These symptoms were aggravated at night after work. On admission, physical examination showed a clear breathing sound without wheezing. Laboratory data revealed WBC count, 9,900/ μL ; ESR, 10 mm/hr ; CRP, negative ; RA factor, negative ; total eosinophil count, 177/ μL ; serum IgE-PRIST, 406 IU/ml ; blood cobalt level, negative.

A skin prick test including 60 common inhalant allergens and cobalt up to 100 mg/ml showed negative results. An intradermal skin test with 10 mg/ml and 100 mg/ml $CoSO_4$ solution demonstrated positive responses respectively(13X12/40X32, 20X15/40X37 ⟨mm⟩, histamine 16X14/64X50). A patch test including nickel, cobalt and chrome demonstrated a negative result. A chest X-ray on admission revealed no abnormal findings. On pulmonary function test, FEV_1 was 3,670 ml(116% of predicted value), FVC was 3,860 ml(103% of predicted value) and FEV_1/FVC was 95%.

A bronchoprovocation test was performed as described previously(Park et al., 1994). $CoSO_4$ in NaCl solutions were administered via a DeVilbis 646 nebulizer. 10 mg/ml $CoSO_4$ did not induce any change of FEV_1. Two minutes tidal breathing of 100 mg/ml $CoSO_4$ solution(38 mg Co inhaled) induced an isolated late asthmatic response and systemic symptoms including generalized weakness, fever, chilling and myalgia were noted 10 hours after inhalation and they continued for several hours(Fig. 1). Although the initial methacholine challenge test showed a negative result, the following methacholine challenge test which was done 24 hours after the cobalt challenge testing showed a positive result at 2.5 mg/ml, and then converted to a negative response on the 7th day after the challenge test(Fig. 2).

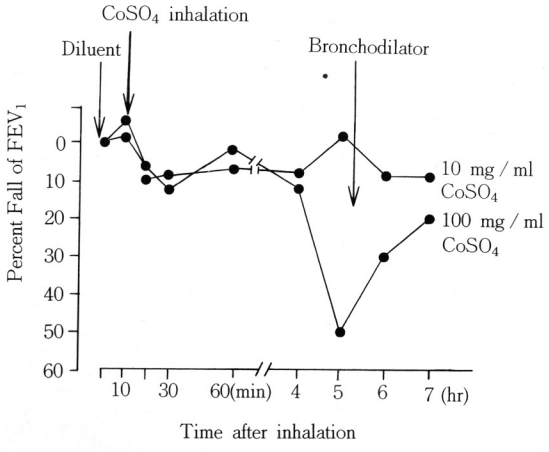

Fig. 1. Result of bronchoprovocation test with $CoSO_4$

Bronchoalveolar lavage fluid analysis which was done after cobalt inhalation challenge testing had 7% neutrophils, 8% lymphocytes, 82% macrophages and 3% eosinophils. The patient was recommended to leave his workplace and he has complained of no more respiratory symptoms.

DISCUSSION

Cobalt has been known to induce occupational asthma(Bruckner, 1967 ; Davison et al., 1983 ; Gheysens et al., 1986 ; Kusaka et al., 1990 ; Shirakawa et al., 1992 ; Cugell, 1992 ; Swennen et al., 1993), hypersensitivity pneumonitis(Sjogren et al., 1980 ; Davison et al., 1983), and pulmonary fibrosis(Davison et al., 1983 ; Demedts, 1984 ; Van Custem, 1987 ; Cugell, 1992) in exposed workers. The prevalence of occupational asthma in a plant using hard metal was 5.6% by a respiratory questionnaire and spirometry (Kusaka et al., 1990). The relationship between these different diseases is still controversial. The present study revealed that cobalt could be a causative agent

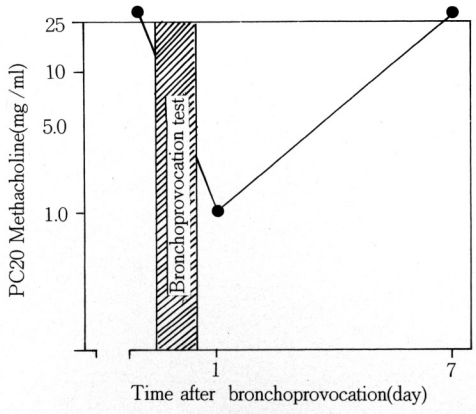

Fig. 2. Changes of methacholine PC20 before and after cobalt-bronchoprovocation test

inducing occupational asthma accompanied by systemic symptoms such as febrile sensation, generalized weakness and myalgia in an employee working in a glass-ware making factory. The latent period to induce cobalt-induced occupational asthma ranged from less than one year to more than 5 years. In fifty eight percent of cases it was less than 1 year(Kusaka et al., 1990). In this study, the patient had begun to experience respiratory symptoms after 11 months' exposure.

Specific bronchoprovocation test has been known as the golden standard for diagnosing occupational asthma(Cartier, 1994), Three patterns of asthmatic response on specific bronchoprovocation test have been described(Perrin et al., 1991). Kusaka et al.(1990) reported 13 occupational asthma patients who undertook bronchoprovocation test with cobalt : four immediate asthmatic responders, five late asthmatic responders, and four dual asthmatic responders. The exact challenge method and allergen concentration inhaled for cobalt-bronchoprovocation test has been unknown. Swedish TLV for cobalt has been 0.1mg/m^3(Sjogren et al., 1980). The concentrations used in the specific bronchoprovocation test ranged from 10^{-5} to 1% $CoCl_2$ solution(Shirakawa et al., 1989, 1990). In the present study, the patient demonstrated an isolated late asthmatic reaction 5 hours after the inhalation and systemic symptoms developed 10 hours after the inhalation.

Most patients with occupational asthma have increased airway hyperresponsiveness(Lam et al., 1979). Seven of eight hard metal workers with asthma had a positive methacholine bronchial challenge test result(Shirakawa et al., 1989). There have been a few case reports of occupational asthma without airway hyperresponsiveness(Park et al., 1990 ; Stanescu and Frans, 1992 ; Park et al., 1994). Significant changes of airway hyperresponsiveness after the specific bronchoprovocation test could be helpful to diagnose these patients. In this study, although the initial methacholine bronchial challenge test demonstrated a negative result, the following methacholine challenge test after exposure to the causative agent demonstrated the development of airway hyperresponsiveness which recovered 7 days later. This result suggested that a negative methacholine challenge test did not necessarily preclude the diagnosis of occupational asthma induced by cobalt.

The mechanism responsible for this asthmatic response should be elucidated. Shirakawa et al.(1988) suggested that an immunologic IgE mediated mechanism might be responsible for the development of hard metal asthma. Kusaka(1993) detected serum specific IgE antibodies against metal-human serum albumin conjugates in sensitized patients. It was unlikely that the immunologic mechanism was responsible in this patient. The skin prick test up to 100 mg/ml $CoSO_4$ showed a negative result, although we did not try to detect serum specific IgE antibody to cobalt. Four of 10 atopic and non-atopic controls showed a positive(>10 mm wheal sized) response on intradermal test with 10 mg/ml and four of them, with 100 mg/ml $CoSO_4$, which suggested a non-specific reaction.

Cobalt has also induced hypersensitivity pneumonitis in exposed workers(Davison et al., 1983 ; Sjogren et al., 1980). Some patients with occupational asthma have suffered from systemic symptoms as well as respiratory symptoms(Park et al., 1991 ; Park et al., 1991). In this study, systemic symptoms were noted 10 hours after the $CoSO_4$ inhalation with asthmatic symptoms. There was no evidence of hypersensitivity pneumonitis in the laboratory tests and bronchoalveolar lavage fluid analysis. Bronchoalveolar neutrophilia(>20% of total cells) in late asthmatic responders at 2 and 8 hours after toluene diisocyanate inhalations was noted by Fabbri et al(1987). In the present study, neutrophil counts in BAL fluid is increased(7%) in comparison to normal controls. Further studies are needed to investigate the role of neutrophils in the pathogenesis of late asthmatic response induced by cobalt.

Cessation of exposure results in considerable improvement or complete resolution in occupational asthma patients and their asthmatic symptoms usually can be easily controlled by eliminating exposure plus drug therapy including bronchodilator and corticosteroids(Cugell, 1992). In this study, the patient was recommended to leave his workplace and is no longer exposed to cobalt. He has complained of no more respiratory or systemic symptoms since complete avoidance.

In conclusion, cobalt can induce occupational asthma associated with systemic symptoms. The possibility of hypersensitivity pneumonitis could not be excluded.

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