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Significant Changes of Bronchial Responsiveness to Methacholine after Early Asthmatic Reaction to Toluence Diisocyanate (TDI) in a TDI-sensitive Asthmatic Worker

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Current asthma is often diagnostically excluded by the presence of normal bronchial responsiveness. We report on a TDI-induced occupational asthma patient with normal bronchial responsiveness. He had suffered from shortness of breath during and after TDI exposure for several months. His initial methacholine bronchial challenge test showed a negative response. The bronchoprovacation test with TDI showed an isolated immediate bronchoconstriction. The following methacholine bronchial challenge tests revealed that the bronchial hyperresponsiveness developed seven hours after the TDI challenge (methacholine PC_{20}:5.1 mg/ml), progressed up until 24 hours, and returned to normal on the seventh day. This case provides evidence that the response of the airway to TDI may not always be accompanied by bronchial hyperresponsiveness to methacholine. Screening programs utilizing methacholine challenges may not always identify TDI-sensitized asthmatic workers.

Key Words: *Toluene diisocyanate, Occupational asthma, Bronchial hyperresponsiveness.*

INTRODUCTION

Toluene diisocyanate (TDI) is a chemical used mainly in the production of polyurethan foams, but also in adhesives, insulation, lacquers, spray paints, elastomers, textile components, and wire coatings. There have been a number of pulmonary reactions attributed to TDI including bronchial asthma (Maxon, 1964; Munn, 1965; Pepys et al., 1972; Charles et al., 1976; Fink and Schleuter, 1978). Both immunological and non-immunological mechanisms have been ascribed to TDI-induced asthma (Taylor, 1970; Porter et al., 1975; Butcher et al., 1977; Butcher et al., 1977; Karol et al., 1978).

The majority of patients with symptomatic occupational asthma have demonstrable non-specific bronchial hyperreactivity (Lams et al., 1979). Some investigators reported several cases of occupational asthma caused by TDI without non-specific bronchial hyperreactivity (Fink and Schleuter, 1978; Hargreave et al., 1980; Stanescu and Frans, 1982). We reported on the asthmatic workers employed in dye industries who had a positive response on Black GR-bronchoprovocation test but negative methacholine challenges (Park et al., 1990). Recently, Malo et al. (1989) noted that significant changes in PC_{20} methacholine after isolated immediate bronchospecific reactions caused by TDI in TDI-sensitive asthmatic patients.

The present report describes our experience with a sensitized worker who demonstrated a positive bronchial challenge test to TDI, but had a negative methacholine bronchial challenge test. Also, changes of bronchial responsiveness to methacholine by TDI challenge were observed.

Case summary

The patient was a 24-year-old male, a smoker with no previous history of atopy, who was admitted to the Department of Chest Medicine, National Medical Center. Five years ago, he had been employed at a company for five months that manufactured furniture.

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During that time, he worked as a painter and was exposed to TDI from a nearby spraying operation. Because he began experiencing shortness of breath and coughing after three months of exposure, he stopped working there. For the last three years, he has been working as a boilermaker and experienced shortness of breath whenever he has been exposed to wall painting. Seven days prior to admission, he worked in a room where he was exposed to spraying paint for three days. Severe dyspnea was developed after the work and became progressively more severe. On admission, chest auscultation revealed severe inspiratory and expiratory wheezing on whole lung field. He was treated with aminophylline, B2-agonist and corticosteroid. After seven days, his respiratory symptoms markedly improved and clear breathing sounds were audible.

Skin prick tests demonstrated immediate positive reactions to house dust (3×3/30×28<mm>). Dermatophagoides farinage (D. farine, 1×1/22×20 <mm>). Dermatophagoides pteronyssinus (4×3/30×24<mm>), and response to TDI-human serum albumin (HSA) conjugate. Total IgE level by PRIST was 374 IU/ml. RAST to D. farinae and D. farinae and D. pteronyssinus showed a negative result.

Bronchoprovocation test with TDI and D. farinae

The bronchoprovacation test was performed according to the previous study (Lee et al., 1989). A phenolized saline solution was inhaled for two minutes with a tidal breathing from a nebulizer 646 (Devilbiss Co. Somerset, Penn.) with compressd air source. In the case of the TDI bronchial challenge test, the subject was asked to breathe the smell from the TDI solution contained in a large beaker for two minutes. The forced expiratory volume in one second (FEV1) and peak expiratory flow rate (PEFR) were measured with a spirometer (Spirotron II, Jaeger, Germany) before and 10 minutes after inhalation. Then, the FEV1 and PEFR were measured frequently during the first hour, and pulmonary function test were performed every hour for seven hours after the chllenge. As shown in Fig. 1., an isolated asthmatic response was observed after the TDI challenge. In the D. farinae bronchoprovocation test, 1:1000 w/v of D. farinae solution was delivered by a nebulizer 646 (Devibies Co.) and inhaled for two minutes with a tidal breathing. Following pulmonary function test was performed in the same way. As shown in Fig. 2, D. farinae-broncho provocation test showed a negative response.

Inhalation challenge with methacholine

Airway responsiveness to methacholine aerosol was performed according to the previously descirbed

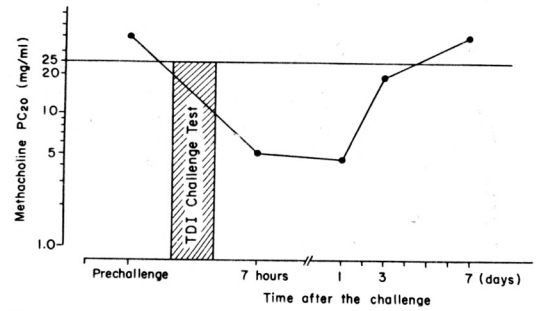

Fig. 1. Result of toluene diisocyanate (TDI) bronchial challenge test

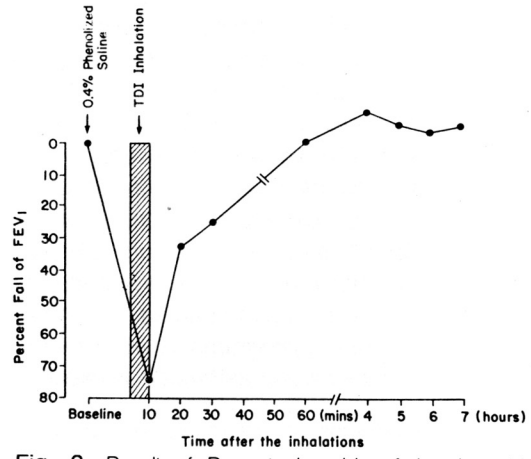

Fig. 2. Result of Dermatophagoides farine bronchial challenge test

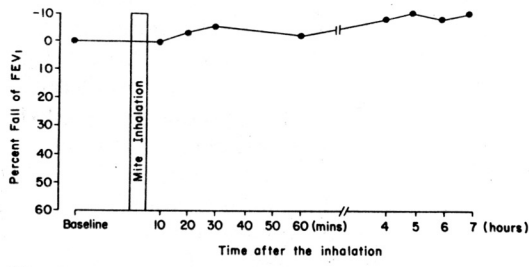

Fig. 3. Changes of bronchial responsiveness to methacholine before and after toluene diisocyanate (TDI) bronchial challenge

method (Chai et al., 1975). In the patient studied, methachline challenges were performed one day before and seven hours, 24 hours, 72 hours and seven days after the TDI challenges. As shown in Fig. 3, the initial methacholine bronchial challenge test was negative. The following methacholine bronchial challenge test revealed that bronchial hyperresponsiveness to

methacholine developed at seventh hour (PC_{20} methacholine:5.1mg/ml), progressed at the 24th hours (to 4.5mg/ml), improved on the third day (20mg/ml), and recovered to normal bronchial responsiveness on the seventh day after the TDI challenge.

DISCUSSION

The worker studied has a clinical presentation of TDI-sensitive occupational asthma without bronchial hyperresponsiveness as other investigators have reported (Hargreave et al., 1980; Stanescu and Frans, 1982). Butcher et al. (1977) reported that only eight of 11 TDI-sensitive asthmatic workers showed positive methacholine challenge tests, and O Brien et al. (1979) noted increased bronchial reactivity to histamine in only 17 out of 31 asthmatic subjects sensitive to TDI. These findings are an interesting observation, since the question occurs as to whether airway hyperreactivity predisposes an individual to TDI-induced asthma and also as to whether it is present before the development of clinically overt asthma. It is suggested that careful inquiry about whether he has ever experienced respiratory symptoms at workplace is needed to identify TDI-induced occupational asthma patients whose initial methacholine challenge tests are negative. Negative methacholine challenge results cannot be used to exclude occupational asthma.

The mechanism which would explain the airway response to TDI cannot be ascertained from this study. Immunologic mechanisms causing TDI induced asthma is probably operative in a small percentage of sensitized workers (Butcher et al., 1983), and another non-immunologic mechanisms were suggested (Bruckerner et al., 1968). The individual in the present investigation was not atopic asthma patient, as confirmed by D. farinae-bronchoprovocation test. A skin prick test with TDI-HSA conjugate was negative. These findings suggested that non-immunologic mechanism might be operative in his asthmatic symptoms.

Changes in bronchial responsiveness to histamine or methacholine have been observed after late or dual asthmatic reactions with common inhaled allergens (Cockeroft et al., 1977; Cartier et al., 1982) or occupational allergens (Cockcroft et al., 1979; Cartier et al., 1984). The inflammation that accompanies late bronchoconstriction is assumed to be responsible for such changes (Hargreave et al., 1980; Mapp et al., 1986; Fabbri et al., 1987). Several studies (Cockcroft et al., 1977; Cartier et al., 1982; Mapp et al., 1986) have demonstrated that isolated immediate reactions after exposure to common allergens and to low molecular weight chemicals do not induce significant changes in nonallergic bronchial responsiveness. However, Fabbri et al. (1987) described one subject who showed an isolated immediate response, but had a change in methacholine PC_{20} two hours after TDI exposure. Malo et al. (1988) described two patients who demonstrated isolated immediate bronchoconstrictions, but had very significant changes in methacholine PC_{20}. In this study, the patient showed early asthmatic response on the TDI bronchoprovocation test, but nonspecific bronchial hyperreactivity developed in seven hours after the bronchoprovocation test and disappeared on the seventh day. The mechanism that developed bronchial hyperresponsiveness in this worker is unclear. Chester et al. (1989) concluded that TDI asthma was caused both by specific and non-specific mechanisms which were partly dependent upon the dose-tested as well upon coexistent host factors. O'Butcher et al. (1976) showed lack of response to TDI vapors in an individual at concentrations of 0.005 ppm but a dual response at 0.01 ppm. It might be possible that more prolonged exposure to TDI in this patient would have induced late asthmatic response.

The example of this case is relevant for the management of subjects with occupational asthma. It might be tempting not to change the workplace in individuals who demonstrated an isolated immediate bronchoconstriction to challenges in the laboratory. Indeed, it can be argued that this reaction can be reversed by the use of bronchodilators and it does not lead to airway inflammation, making unlikely that these sub jects will develop permanet asthma once they stop working. As this study suggests, close and serial monitering of bronchial responsiveness might demonstrate that significant changes occur in the laboratory and workplace.

In conclusion, TDI-induced occupational asthma can occur when methacholine bronchial responsiveness is normal and an isolated immediate asthmatic response induced by TDI might lead to nonspecific bronchial hyperreactivity.

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