

Bronchial hyperresponsiveness, airway inflammation and occupational asthma induced by toluene diisocyanate

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INTRODUCTION

Sensitized subjects may develop symptoms of asthma after exposure to isocyanates in their place of work (1, 2). After challenges with isocyanates in the laboratory, sensitized subjects develop immediate, late and dual asthmatic reactions (3). Dual and late asthmatic reactions are more frequent than early asthmatic reactions after challenge with isocyanates (4), and like allergen induced dual and late asthmatic reactions, have probably more relevance to the natural history of asthma than do the immediate asthmatic reactions. In fact, late asthmatic reactions are ususally more severe, last longer, respond to steroids but not to bronchodilators, are more resistant to therapy, and subjects sensitized to TDI who develop a dual or late asthmatic reactions continue to have asthma upon cessation of exposure (5). Longitudinal studies suggest that the majority of subjects with occupational asthma continue to have persistent asthma and airway hyperresponsiveness several months and years after the cessation of exposure. The mechanisms of late asthmatic reaction and of persistence of asthma after cessation of exposure are unknown.

We speculated that toluene diisocyanate (TDI) might cause late asthmatic reactions and increase bronchial responsiveness by causing an acute inflammatory reaction in the airways, and that airway inflammation may be responsible for both the transient and the long-lasting airway hyperresponsiveness which is associated with the persistence of occupational asthma induced by isocyanates.

ASTHMATIC REACTIONS, AIRWAY HYPERRESPONSIVENESS AND AIRWAY INFLAMMATION INDUCED BY TDI

To test these hypotheses, we examined sensitized subjects during asthmatic reactions induced by exposure to toluene diisocyanate in the laboratory. We observed that late and dual, but not early, asthmatic reactions are associated with a transient increase of bronchial responsiveness (6) and, at the same time, with an increase of neutrophils followed by eosinophils (7), and of LTB₄ (8) and albumin (7) in bronchoalveolar lavage fluid. Late asthmatic reactions, increased bronchial responsiveness, and increase of neutrophils, eosinophils, LTB₄ and albumin concentration in bronchoalveolar

lavage induced by exposure to TDI are all prevented by pretreatment with prednisone (9) but not with the nonsteroidal antiinflammatory agent indomethacin (10). Aerosolized steroids alone e.g. beclomethasone (11, 12), desamethasone isonicotinate (13), or combined with salbutamol (14) completely inhibit late asthmatic reactions induced by TDI, whereas theophylline (11) has a partial, and verapamil (11), ketotifen (15), salbutamol alone (14), atropine (16) and cromolyn (11) have no protective effect. All these studies, taken together, support the hypothesis that in the late and dual, but not early, asthmatic reaction induced by TDI, bronchoconstriction and airway inflammation are involved, and that polymorphonuclear leukocytes are required for hyperresponsiveness to occur. Although one of the inflammatory mediators (i.e. LTB₄) has been measured during late asthmatic reactions induced by TDI, the identification of the structure and of the source of all chemotactic factors which attract neutrophils and eosinophils in the airspaces, and the identification of the mediators released by these cells remains to be established.

PATHOLOGY OF TDI ASTHMA

Only one report is available on documented occupational asthma death induced by a low exposure to isocyanate at work in a subject previously demonstrated to be sensitized to toluene diisocyanate (17). Lung pathology included some characteristic features almost invariably reported in status asthmaticus and some findings different from previous reports on non-occupational asthma. Macroscopically, lungs appeared overinflated and did not collapse on opening of the pleural cavities. The airways were plugged with mucus containing abundant exudate. Microscopy showed morphological abnormalities of both airways and lung parenchyma. In the airways, extensive epithelial desquamation, edema of the bronchial wall, diffuse infiltration of inflammatory cells including eosinophils and neutrophils and marked thickening of the basement membrane were observed in addition to the almost pathognomonic presence of extensive plugging of the bronchioles. Mucous glands were hyperplastic and bronchial smooth muscle were hypertrophic and disarrayed with loss of the usual regular intersections of fibers that criss-cross each-other unevenly and form whirls. While hypertrophy of airway smooth muscle was almost invariably present in previous reports on non-occupational asthma, the disarray of smooth muscle fibers had not been described before. Abnormal in-vitro responsiveness of airway smooth muscle after exposure to isocyanates has been reported in an animal model (18). In addition a contractile effect of TDI on smooth muscle from different sources has been recently demonstrated in vitro, and it seems to be mediated by the release of tachykinins (Mapp, personal communication). Although the study of McKay and Brooks did not include a morphologic description of the tissue, the disarray of smooth muscle fibers observed in asthma death due to isocyanates suggests that this chemical may directly affect airway smooth muscle.

Morphologic abnormalities were present not only at the bronchial level, but

also within the alveolar walls. Areas of acute emphysema alternated with focal areas of atelectasis were observed. The presence of acute emphysema was confirmed by the observation of alveolar wall destruction, which appeared as fragments of septa floating in the alveolar spaces. These areas of focal destruction were adjacent to areas of perfectly intact alveolar walls. Interestingly, these focal lesions have not been described in non-occupational asthma, and are very similar to the parenchymal abnormalities observed in the early stage of emphysema in a group of smokers in whom the classic indices of emphysema were still normal (19, 20). This observation needs to be verified with more complete studies. It could be important, however, to better clarify this point, since some investigators have recently described a possible role of the loss of elastic recoil in the pathogenesis of asthma (21). The elastic loads against which bronchial smooth muscle contracts are important determinants of the degree of airway narrowing, and alveolar walls destruction, together with bronchial wall edema, may facilitate airway narrowing by decreasing these elastic loads. Acute alveolitis may develop in subjects sensitized to methyldiphenyl diisocyanate after a specific inhalation challenge (22). Polymorphonuclear infiltration of the alveolar walls is present in asthma death due to isocyanates, suggesting that, at variance with asthma death induced by allergens, death induced by isocyanates in sensitized subjects may be associated with parenchymal injury.

AIRWAY HYPERRESPONSIVENESS AND PROGNOSIS OF TDI INDUCED ASTHMA

Among the pathologic features observed in the airways, the eosinophilic infiltration of the mucosa and submucosa was particularly pronounced (17). Interestingly Paggiaro et al (23) recently reported that subjects with persistent asthma after cessation of exposure have chronic inflammation of the airway mucosa, characterized by slight infiltration of eosinophils. Indeed, longitudinal studies suggest that the majority of subjects with occupational asthma continue to have persistent asthma months and years after the cessation of exposure (24). We recently completed a follow up study (25) on 35 subjects with different type of reaction at the inhalation challenge, and observed that the few subjects who recovered, in addition to be younger and to have a shorter duration of exposure and disease, developed either an early or a dual asthmatic reaction at the screening inhalation challenge with TDI, whereas none of the subjects who continued to be exposed and/or developed a late asthmatic reaction at presentation recovered completely. The subjects with a dual asthmatic reaction who recovered had a milder reaction compared to those subjects who had a dual asthmatic reaction at presentation and who did not recover.

Whether the recovery (or failure to recover) is related to the degree of airway inflammation remains to be established, but the results of our study combined with the results of several other studies strongly suggest that this might be the case. Interestingly in all the longitudinal studies published so far, subjects who continued to be exposed, even if at presumably lower

concentrations of isocyanates or other sensitizing agents, were the ones who did not recover from occupational asthma.

MECHANISM OF ACTION OF ISOCYANATES: neurogenic inflammation induced by toluene diisocyanate

Several mechanisms of action of isocyanates have been explored (2). Recently Sheppard et al (26) have shown that tachykinins may play a critical role in the increase in in-vivo responsiveness of airway smooth muscle that follows exposure to TDI in guinea pigs, and that this effect may be due both to release of tachykinins and to inhibition of neutral endopeptidase, a cell membrane bound enzyme that cleaves tachykinins (27). In recent experiments, we have confirmed the role of tachykinins in the mechanism of action of TDI by showing that toluene diisocyanate contracts smooth muscle in vitro through the activation of the "efferent" function of capsaicin-sensitive primary afferents neurons (28-30). In addition we have shown that both Ruthenium Red, a drug that acts as a selective capsaicin antagonist, and indomethacin, a classic PGs synthesis inhibitor, inhibit TDI-mediated effects on sensory neurons (31), suggesting that the effect of toluene diisocyanate is presumably indirect. These experimental studies suggest a novel mechanism of action of TDI which, however, need to be examined in humans.

Acknowledgment

We sincerely thank the subjects who contributed to these studies. We also acknowledge the technical assistance of Luigi Zedda and thank Licia Tolin and Susan Lees for reviewing and editing the manuscript.

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