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Toluene di-isocyanate-induced asthma

I. Reactions to TDI, MDI, HDI and histamine

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Summary

A group of twenty-four workers handling di-isocyanates and with respiratory disease were investigated by occupational-type bronchial provocation tests for sensitivity to toluene di-isocyanate (TDI), to which all were exposed, and to diphenylmethane di-isocyanate (MDI) and hexamethylene di-isocyanate (HDI). Sixteen gave asthmatic reactions to TDI and eight of these also reacted to MDI. Four of the eight TDI and MDI reactors had histories of exposure only to TDI, and of them two reacted also to HDI. Of nine subjects tested with HDI, three gave asthmatic reactions, and all three also reacted to TDI and MDI. Thus reactions to MDI and HDI were elicited only in the TDI reactors. The possibility of specific sensitivity to these and other di-isocyanates requires tests in subjects exposed to them and not to TDI.

Introduction

The respiratory hazards of di-isocyanates are well known and most attention has been given to toluene di-isocyanate (TDI), which is sufficiently volatile to give rise to measurable atmospheric concentrations at room temperature. Less volatile agents such as diphenylmethane di-isocyanate (MDI) and certain polyisocyanates are being tried as substitutes. Respiratory disease associated with MDI (Longley, 1964; Munn, 1965; Tanser, Bourke & Blandford, 1973) has been reported, but it is considered safer.

The only prospective study to date shows that 'sensitization' occurs most commonly after regular exposure to higher atmospheric concentrations of TDI. Control or decrease of exposure is likely to result in less frequent 'sensitization'.

In this study occupational-type inhalation tests were made in twenty-four subjects occupationally exposed to one or more di-isocyanates to see if there was evidence of 'sensitivity' to more than one.

Materials and methods

All twenty-four male workers gave a history of occupational exposure to TDI,

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fourteen to MDI and six to HDI, of whom five had also been exposed to all three di-isocyanates. They were referred for investigation of possible work-related respiratory symptoms.

Isocyanate inhalation tests

Control tests. All challenges were made in a 6·0 m^3 closed cubicle. Control tests for TDI testing consisted of painting for 30 min with a varnish not containing TDI. FEV_1 and FVC were recorded prior to and following challenge at 5 min intervals for the first 30 min, at 10 min intervals for the next 30 min and then hourly for at least 8 hr.

As controls for the MDI and HDI testing the FEV_1 and FVC were recorded hourly from 10.00 to 22.00 hours without any challenge until a stable control day was achieved.

On test days with TDI, MDI or HDI, recordings of FEV_1 and FVC were made as for the TDI control test.

Tests for TDI 'sensitivity'. All twenty-four subjects were tested with TDI by painting with the varnish plus TDI. The atmospheric concentration in the cubicle was measured by a model 700 UEI monitor. The starting concentration was $\leqslant$0·001 p.p.m. and if no asthmatic reaction occurred, the concentration was gradually increased on subsequent days to a maximum of 0·02 p.p.m.

Tests for MDI 'sensitivity'. All twenty-four subjects were tested with MDI. The UEI meter readings of the atmospheric concentration were multiplied by 1·4 to give the MDI concentration. Challenges were made by heating Desmodur VL which contains mainly monomeric diphenylmethane di-isocyanate or 1·0 g of crystalline MDI at 110°C. The atmospheric concentration was adjusted by the period of heating starting at $\leqslant$0·001 p.p.m., increasing to a maximum of 0·02 p.p.m. on subsequent days if no asthmatic reaction occurred.

Tests for HDI 'sensitivity'. These were made on nine subjects. The method involved painting Desmodur N (Bayer), containing a maximum concentration of free HDI of 0·7%, on a surface for 30 min. Atmospheric concentrations were not measured.

A positive reaction was taken as a fall in FEV_1 of 15% more than on the control day.

Histamine inhalation tests

Bronchial reactivity to inhaled histamine acid phosphate was assessed in all twenty-four subjects. Doubling concentrations (0·25–32 mg/ml) of an aerosol were inhaled for 30 sec at 5 min intervals until a fall in FEV_1 of 20% occurred or until the maximum concentration was reached. Bronchial hyper-reactivity was considered to be present if a 20% fall in FEV_1 occurred.

Results

TDI tests (Table 1)

Asthmatic reactions were elicited in sixteen out of twenty-four subjects by atmospheric concentrations of TDI ranging from $\leqslant$0·0001 to 0·02 p.p.m.; five gave non-immediate (late) reactions only and eleven gave combined (dual) reactions.

MDI tests

Asthmatic reactions were elicited in eight out of twenty-four subjects by atmospheric concentrations of MDI ranging from $\leqslant$0·0014 to 0·014 p.p.m. Of these four gave

Table 1. Twenty-four subjects tested with TDI and MDI (nine also with HDI): previous exposure and pattern of asthmatic reaction

Subject	TDI Prior exposure	Reaction	MDI Prior exposure	Reaction	HDI Prior exposure	Reaction
(1) A.B.	+	Dual	−	Dual	−	n.t.
(2) K.D.	+	Dual	−	Immediate	−	Non-immediate
(3) F.L.	+	Dual	−	Immediate	−	n.t.
(4) L.W.	+	Dual	−	Immediate	−	Immediate
(5) W.C.	+	Dual	+	Immediate	+	n.t.
(6) W.L.	+	Dual	+	Dual	+	Negative
(7) B.S.	+	Dual	+	Dual	+	Non-immediate
(8) L.L.	+	Non-immediate	+	Dual	−	n.t.
(9) J.H.	+	Dual	−	Negative	+	n.t.
(10) C.J.	+	Dual	+	Negative	+	Negative
(11) M.R.	+	Dual	+	Negative	+	Negative
(12) J.W.	+	Dual	+	Negative	−	n.t.
(13) W.Ca.	+	Non-immediate	−	Negative	−	n.t.
(14) R.G.	+	Non-immediate	−	Negative	−	n.t.
(15) L.Le.	+	Non-immediate	+	Negative	+	n.t.
(16) D.M.	+	Non-immediate	−	Negative	−	Negative
(17) J.B.	+	Negative	−	Negative	+	Negative
(18) J.K.	+	Negative	+	Negative	+	n.t.
(19) T.S.	+	Negative	+	Negative	+	Negative
(20) P.W.	+	Negative	+	Negative	+	n.t.
(21) J. He.	+	Negative	+	Negative	+	n.t.
(22) J.S.	+	Negative	+	Negative	+	n.t.
(23) W.E.	+	Negative	−	Negative	−	n.t.
(24) J.W.	+	Negative	−	Negative	−	n.t.

n.t. = Not tested.

immediate and four gave combined reactions. All eight subjects also reacted to TDI and in four there was no history of known prior exposure to MDI. The atmospheric concentrations of TDI and MDI eliciting reactions in these eight subjects, plotted against histamine reactivity, are given in Fig. 1.

HDI tests

Asthmatic reactions were elicited in three of the nine tested, of whom six were also exposed to HDI. One gave an immediate and two gave non-immediate reactions. All three also gave positive reactions to TDI and to MDI and two had a history of exposure to TDI only, and the third to TDI and HDI and MDI.

On the basis of the isocyanate challenge tests the subjects were divided as follows. Group I: sixteen with asthmatic reactions to TDI; with group Ia having eight reacting

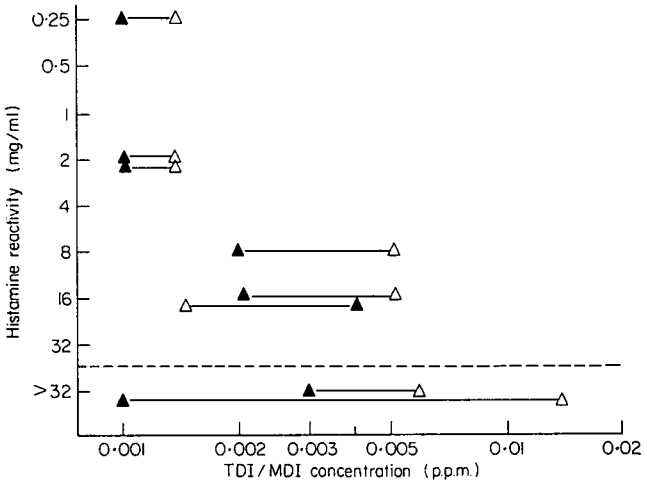

Fig. 1. Asthmatic reactions to TDI (▲) and MDI (△).

to TDI only, of whom one was sensitive to histamine, and group Ib having eight reacting to TDI and MDI (of whom six were sensitive to histamine and 3 gave asthmatic reactions to HDI in addition). Group II: eight in whom no asthma was elicited, of whom five were sensitive to histamine.

Histamine inhalation tests

The histamine reactivity is plotted against the atmospheric concentrations of TDI eliciting asthmatic reactions in groups Ia and Ib and group II (Fig. 2).

Discussion

In this study eight of the sixteen subjects with asthmatic reactions to TDI reacted to MDI, and three of these eight also reacted to HDI. Of the eight with asthmatic

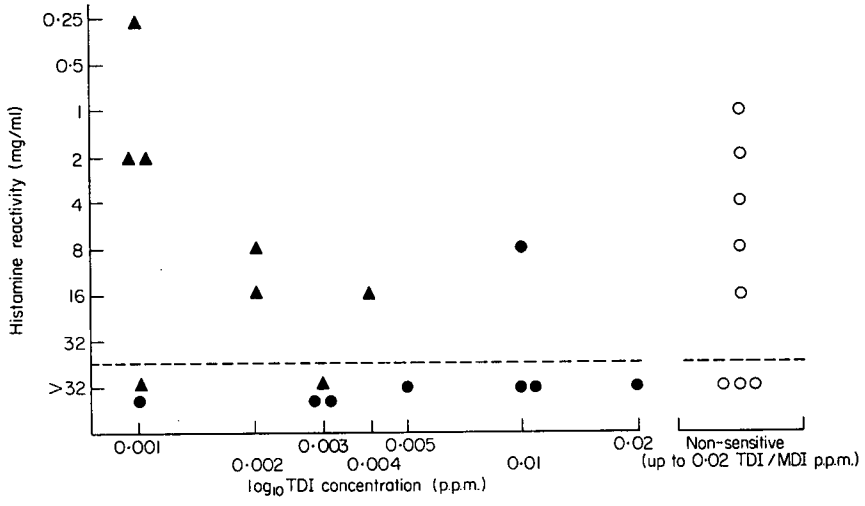

Fig. 2. Histamine reactivity *vs* TDI reactivity. (▲) TDI and MDI ($n=8$) sensitive; (●) TDI-sensitive ($n=8$); (○) non-sensitive ($n=8$).

reactions to MDI, four had not previously been exposed as far as they knew, and this applied also to two of the three subjects reacting to HDI. Among the possible explanations for these findings are cross-reactivity between the different isocyanates, an irritant or pharmacological effect in subjects with hyper-reactive airways, or both. In isocyanate-induced asthma attributed to a specific hypersensitivity reaction, the most likely explanation is that the isocyanate or a derivative acts as a hapten (Karol, Ioset & Alarie, 1978). The molecular structures of TDI, MDI and HDI are, however, dissimilar, making cross-sensitivity unlikely, although more final interpretation must await the characterization of the isocyanate reactant. This may now become possible because of the demonstration of tolyl-specific IgE antibodies in workers sensitive to TDI (Karol *et al.*, 1978).

Those reacting to more than one isocyanate, group Ib, had a greater degree of histamine reactivity and reacted to lower concentrations of TDI than those reacting only to TDI, group Ia. This suggests that, even at very low concentrations, isocyanate-induced asthma could be the result of irritant or pharmacological actions of hyper-reactive airways. The main argument against this is the presence of a comparable degree of histamine reactivity in the eight negative reactors, group II, and the very low concentrations capable of eliciting reactions.

A third, and the most likely, explanation is that there may be a combination of specific hypersensitivity to TDI with an increase in non-specific bronchial reactivity. Following reactions to antigen challenge, increase in non-specific bronchial reactivity may occur although the FEV_1 and FVC have returned to pre-challenge levels (Cockroft et al, 1977). It is possible that in our subjects with asthmatic reactions to more than one di-isocyanate the asthmatic reaction to TDI challenge was based on hypersensitivity but that subsequent positive reactions to MDI or HDI may have resulted from an increase in non-specific bronchial reactivity thus favouring reactions to MDI and HDI, albeit in low concentrations.

Thus in some subjects sensitized to TDI asthmatic reactions can be elicited by other di-isocyanates, whatever the mechanism, and clinical asthma may not be prevented simply by changing the nature of the di-isocyanate. One cannot be sure whether or not the TDI reactors met the other di-isocyanates at work and in this way provided a basis for multiple sensitivity. Studies of subjects known to be specifically exposed to individual di-isocyanates may give answers to these questions.

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