

Cross-reaction between aromatic isocyanates (TDI and MDI): a specific bronchial provocation test study

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Summary

A study was performed on twenty-five workers exposed to polyurethane varnishes exclusively catalysed with TDI, who developed asthma to this substance. The aim of the study was to establish, using bronchial provocation tests, whether a cross-response to MDI exists. The results were positive but no definitive evidence has been reached because there was cross-response in only 48% of cases. It is interesting, however, that cross-responders did not predominate among the subjects with a late reaction to TDI ($P=0.0038$), whereas cross-responders were in the majority among the subjects with a dual reaction to TDI ($P=0.0334$). It is possible that the pattern of the asthmatic reaction to BPT with TDI influences the cross-reaction to other isocyanates.

Introduction

Isocyanate asthma is a well-known disease, particularly associated with toluene-diisocyanate (TDI) hypersensitivity, but there are also reports on asthma due to other isocyanates, both aromatic, e.g. diphenylmethane-isocyanate (MDI) and naphthylene-diisocyanate (NDI), and linear, e.g. hexamethylene-diisocyanate (HDI). In modern industry TDI tends to be replaced by the less volatile MDI in an attempt to reduce the risk of professional inhalation during the use of polyurethane glues and varnishes, and in the manufacture of articles in rigid or expanded polyurethane foam.

From the point of view of prevention, attention has been focused on the problem of cross-reactivity between different isocyanates. The allergologic diagnostic approach has been unhelpful [1, 2] because of the uncertain allergic mechanism of isocyanate asthma and the difficulty in obtaining a standardized isocyanate-HSA conjugate. The high reactivity of diisocyanates can indeed cause non-specific binding with proteins and their denaturation.

An alternative approach is based on specific bronchial provocation tests (BPT). Cross-reactivity of TDI-MDI [3, 4] and TDI-HDI [5, 6] has been investigated in the

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past in isolated cases and in a few polyexposed subjects [7-9]. These studies were inconclusive and did not reveal any specific factor responsible for the cross-reaction.

The present study was specifically planned to verify, at the level of the target organ, the existence of a respiratory cross-reaction between TDI and MDI in responsive volunteers occupationally exposed to TDI.

Subjects and methods

In order to reduce the number of cases, the study started as a sequential analysis of the observed responses to the two isocyanates. The BPT responses to TDI and MDI have been scheduled in the tables of Bross [10]. This method allowed us to stop the study as soon as we exceeded the limit of the table, thus ensuring statistical significance.

In this sequential study plan each subject spontaneously underwent BPT with TDI and, if the response was positive, also with MDI. Only after the test with MDI did we consider the next subject. We stopped the study at a statistical significance of $2\alpha = 0.1$ and at this stage twenty-five patients had been examined.

The group consisted of twenty-one males and four females, all working in the furniture industry and exposed to polyurethane varnish containing TDI, who had never been in contact with MDI. Exposure to MDI in the subjects examined can be excluded because they had worked only with furniture and in Italy the polyurethane varnish used in the wood industry contains TDI or HDI, but never MDI. We also checked the exposure at work of these selected cases. If there was any doubt the case was excluded from this study.

The patients were examined during a stable period of the disease. A few days before challenge they were evaluated by baseline pulmonary function tests (VC, FEV₁ and FEV₁/VC% with Pulmotest Godart: Utrecht, The Netherlands, or Pneumotest-transferscreen Jaeger: Wuerzburg/Main, FRG), the predicted values being derived from those published by the European Coal and Steel Community [11]. Subjects with a FEV₁ less than 83% of predicted values, or a FEV₁/VC% under the limit predicted by the tables, were considered to be obstructed. Before the challenge we also investigated atopy, defined as one or more positive reactions (weal > 5 mm) to skin-prick tests with eleven common allergens, and non-specific bronchial hyperresponsiveness. This was evaluated with methacholine inhaled from a dosimeter until a fall in FEV₁ exceeding 20% was observed; the provocative dose causing a 20% fall in FEV₁ (PD₂₀ FEV₁) was calculated from the log dose-response curve. In three cases a cold fog response test was performed and the results were not further analysed.

Specific bronchial provocation test with TDI and MDI

Specific bronchial provocation tests were carried out in Siena (fourteen cases) using an 8-m³ cabin, and in Lecco (eleven cases) with a 7-m³ cabin, with a maximum exposure of 15 min. The airborne isocyanate concentration in the cabins ranged from 5 to 20 ppb (parts per billion).

In Siena the challenges with TDI were performed by a direct inhalation of TDI 80/20 vapour [12, 13] and in Lecco by heating 0.5 ml of TDI 80/20 upon a watch-glass at 60°C with a fan in the room. The TDI concentration was evaluated with a MDA 7005 detector in Siena and by direct sampling and evaluation in Lecco (Marcali method—NIOSH P&CAM 141).

We have previously shown that a good correlation exists between the two methods both for TDI [12] and MDI (unpublished data) for a short period of sampling.

The challenges with MDI were performed by heating 3 ml of Desmodur VL or 0.3 mg of crystalline MDI upon a watch-glass at 130–140°C. A fan was used to circulate the air in the room. The 7005 detector or the impinger for the Marcali method (NIOSH P&CAM 142) were placed 60–70 cm from the hot plate, near the patient.

FEV₁ was recorded before, and 15, 30 and 60 min after, the challenge. The measurement was repeated every hour up to 8 hr. A fall in FEV₁ of 15% more than on the control day was considered to be a positive reaction; the responses were classified as immediate (fall in FEV₁ within the first hour after the challenge), late (between the second and the seventh to eighth hour after exposure) and dual (both immediate and late bronchoconstriction). Control tests were performed in all cases with varnish not containing TDI or MDI. It was impossible to conduct the challenges in a correct blind manner because of the different smell of the substances.

The tests with MDI were performed, as far as possible, with the same concentration range as for TDI, and the interval between the two tests was 2–3 days (mainly in Siena) or 2–5 weeks (mainly in Lecco): in this case bronchial hyperresponsiveness was evaluated again before the second BPT.

Statistical analysis

Statistical analysis was performed with the Fisher's exact test, the Wilcoxon paired test, or the Mann-Whitney *U*-test, as appropriate.

Results

Details of the subjects (age, smoking habits, atopic status, baseline ventilatory function, PD₂₀ by the methacholine test, TDI and MDI concentration and patient's reaction to the bronchial provocation test) are shown in Table 1. The patients appear in the chronological order in which they entered the study.

We obtained twelve late, nine dual and four immediate reactions to TDI, and two late, two dual and eight immediate reactions to MDI. This allowed us to end the sequential study at the fixed level of significance, but always within the area of doubt, with no possibility of predicting with certainty the existence of a complete cross-reaction between the two aromatic isocyanates (Fig. 1). None of the patients had a bronchospastic reaction (FEV₁ changes were always < 10% of basal value) during the test with varnish not containing isocyanates.

No statistical difference was found in the isocyanate concentration during the test either in the whole group or between the cross-responder and non-cross-responder subgroups (Wilcoxon test for matched data).

The analysis of bronchial hyperresponsiveness between cross-responders (PD₂₀ Mch: GM 186.2 mcg) and non-cross-responders (PD₂₀ Mch: GM 179.8 mcg) did not show any significant difference (Mann-Whitney *U*-test).

Bronchial obstruction and different time intervals between the TDI and MDI test were uniformly distributed between cross-responders and non-cross-responders ($P=0.449$ and $P=0.429$ by Fisher's test, respectively). In the same way there was no significant difference in bronchial responsiveness before the two tests (Wilcoxon test for matched data).

We also investigated whether the kind of reaction to the TDI provocation test affected the presence of cross-reaction. It turned out that cross-responders predominated among the subjects with a dual reaction to TDI, but were a minority among the

Table 1. Details of the subjects in chronological order of entry to the study

Number	Age (years)	Smoking habits	Atopic status	VC% (predicted)	FEV ₁ % (predicted)	FEV ₁ /VC (predicted)	PD ₂₀ (mcg)	TDI (ppb)	Response	Break (weeks)	PD ₂₀ (mcg)	MDI (ppb)	Response
1	21	—	—	110	107	77.5	230	17.5	Early	0	/	13.5	—
2	60	Ex	—	125	105	59	110	10	Late	0	/	10	—
3	52	+	—	100	98	71.5	1100	11	Late	0	/	12	—
4	33	—	—	114	78	53.5	52	8	Dual	0	/	11	Early
5	48	—	—	98	95	72	115	9	Late	0	/	11	—
6	38	—	—	96	87	69.5	120	20	Dual	4	120	18	Early
7	45	+	—	109	86	59	*	8.5	Dual	4	*	10	Dual
8	25	—	—	92	92	80	*	14.5	Dual	3	*	18	Early
9	21	+	+	104	118	81.5	105	13.5	Dual	0	/	11	—
10	41	—	—	92	105	87	*	15.5	Late	4	*	20	—
11	51	—	—	101	103	75	120	14.5	Late	4	670	20	—
12	21	—	—	109	105	72.5	200	9.5	Late	0	/	9	—
13	22	—	—	97	68	56	80	20	Late	2	100	20	—
14	49	Ex	—	93	61	48	50	7	Late	0	/	10	—
15	42	—	—	107	110	78	625	14	Early	0	/	14.5	Early
16	23	—	—	100	87	70	288	17	Late	4	100	20	—
17	52	Ex	—	94	104	82	500	18	Dual	0	/	16	Late
18	62	—	—	94	100	75	700	16	Dual	0	/	16.5	Dual
19	44	Ex	—	71	74	78	300	17	Late	0	/	15.5	—
20	40	—	—	95	101	80	500	14.5	Late	3	485	16	Early
21	53	—	—	76	54	50.5	70	14.5	Early	2	70	16.5	Early
22	52	—	—	102	95	68	60	20	Dual	4	110	12	—
23	28	—	—	107	95	71	55	10	Early	2	110	18	Early
24	49	—	+	103	103	73.5	175	14.5	Dual	0	/	9.5	Early
25	43	+	—	115	101	66.5	109	16	Late	0	/	11.5	Late

/ = Test not performed.

* = Positive response to fog test.

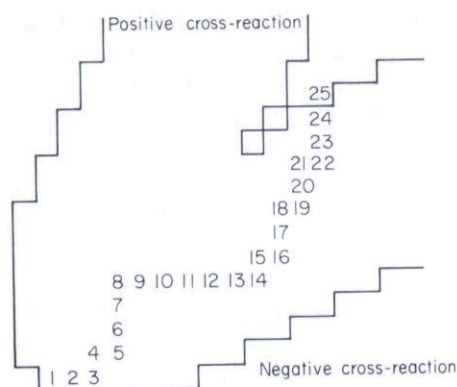


Fig. 1. Bross diagrams [10] were used for the statistical analysis. All patients were set in chronological order until the border of the diagram had been passed.

Table 2. A subdivision of cross-responses based on the response to TDI bronchial provocation test

TDI response	Cross-response of BPT with MDI	
	+	-
Late	2	10
	$P=0.0038$ (Fisher's test)	
Not late	10	3
Dual	7	2
	$P=0.0334$ (Fisher's test)	
Not dual	5	11
Early	3	1
	$P=0.2260$ (Fisher's test)	
Not early	9	12

subjects with a late reaction (Table 2). We found no statistical significance for immediate reactions because of the small number of cases.

In the subjects with early cross-reaction (single early or dual) we compared the magnitude of the bronchoconstriction to TDI (mean FEV_1 fall = 40.8%) and to MDI (mean FEV_1 fall = 40.7%), but there was no difference (Wilcoxon test for matched data). The late cross-reactions were too few to be analysed (mean FEV_1 fall to TDI = 46%, to MDI = 34.7%).

Discussion

In the present study, the principal aspects of bronchial cross-reactivity between two different isocyanates were analysed in a group of painters exposed exclusively to TDI.

Some comments are needed on the different air measurements of isocyanates that were used for their simplicity and swiftness. During the MDI test no aerosol was generated, but it is very difficult to say what the 7005 detector or Marcali method really

measures during BPT with TDI and MDI because both methods are based on a colour-intensity reaction. They have 'fortuitously reasonable overall accuracy' [14], but for isocyanates, particularly HDI and MDI, HPLC analysis is required.

Respiratory cross-reactivity between TDI and MDI was observed in 48% of cases, but it was not possible to draw a final conclusion about the determining factors. It is clear that the bronchial responsiveness of the cross-reacting subjects was no higher than that of the non-reacting subjects. In fact, the two groups did not manifest different PD₂₀ methacholine reactivity. Other factors, such as smoke, atopy and basal ventilatory status did not seem to be of any importance.

In some cases the two BPTs were performed with only a short break (1–2 days) and TDI was always the first substance to be tested. However, it is well known that after a positive BPT, mainly after a late response, an increase of bronchial hyperresponsiveness can be observed and this could influence the response to a further test. In spite of this, we did not find a higher number of cross-reactions between the subjects who underwent the second test immediately after the first one and those who underwent it with a break of 2–5 weeks (when the degree of bronchial hyperreactivity was similar to that of the first BPT). This suggests that the presence or absence of cross-reactivity cannot be attributed to a transitory enhancement of bronchial responsiveness due to a prior positive bronchial provocation test.

In the group studied, however, there was a different pattern in the results of the test with MDI that depends on the type of response to TDI (the only isocyanate to which our patients were occupationally exposed). The majority of the subjects with a dual reaction to TDI were cross-responders to MDI, while the majority of those with a late reaction were not. This was also observed by O'Brien *et al.* [8] who found, in a group of eight asthmatic subjects, that the three having late reactions did not cross-react, whereas four out of five subjects with a dual response did.

A dual response may be due to a greater releasability of mediators, but this needs to be proved. It is also possible that mechanisms other than immune reactions play a role in the immediate component of dual responses to isocyanates. This may be related to the fact that four out of eight dual responders to TDI had only a typical immediate response to MDI. This hypothesis needs to be tested with further studies.

We can therefore conclude that many subjects affected by occupational asthma due to TDI may have specific bronchial reactions when exposed to MDI. The complete evaluation of this cross-reactivity may be useful in the prevention of asthmatic attacks when job location of workers in the polyurethane industry is proposed.

The mechanism of cross-reactions is not yet understood and they cannot yet be predicted. The bronchial provocation test can demonstrate cross-reactions in the laboratory but is of no help in revealing the mechanism of isocyanate asthma.

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