OCCUPATIONAL ASTHMA DUE TO ISOCYANATES IN SINGAPORE

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ABSTRACT

Nine cases of occupational asthma due to isocyanates are described. The isocyanates involved included toluene diisocyanate (TDI), diphenyl-methane diisocyanate (MDI) and polyisocyanates. The importance of asking the occupational history in a patient with asthma is illustrated. The importance of early diagnosis and removal from further exposure is also discussed.

Keywords: asthma, occupational history, TDI, toluene diisocyanate

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INTRODUCTION

Isocyanates are compounds containing one or more isocyanate (NCO) groups which will readily react with various chemical groups in many organic compounds eg. the hydroxyl groups of alcohols and amino, sulphydryl or carboxylic groups in proteins. Isocyanates are widely used in production of a large number of products eg. polyurethane foams (cushions, mattresses, shoe soles etc), insulation material (in refrigerators), surface coatings (varnishes, paints, wire coating), adhesives, binding material in foundry moulds etc.

Occupational asthma due to isocyanates is a well established entity[1-4]. Asthmatic symptoms have been described in workers exposed to the simple diisocyanates eg. toluene diisocyanate (TDI)[5], diphenyl-methane diisocyanate (MDI)[6] or hexamethylene diisocyanate (HDI)[7] and also to the more complex polyisocyanate[8,9]. Cross reaction eg. between TDI and MDI have also been described[10].

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Nine (36%) of the 25 confirmed cases of occupational asthma in the official statistics on occupational diseases of the Department of Industrial Health (as at March 1990) were due to isocyanates. This makes isocyanates the most common cause of occupational asthma among notified cases in Singapore. However the health hazard of isocyanates is still not widely recognised. We report here the 9 cases of occupational asthma due to isocyanates.

CASE REPORTS (Table I)

Case 1

Mdm K was admitted to hospital for an acute asthmatic attack. She was working in a factory manufacturing polyurethane foam products (mattresses, cushions). She had worked there for one and the half years without any symptoms. She had no past history of asthma. A visit to the factory confirmed that TDI was mixed with polyol and a catalyst to make the foam. The mixing was carried out by other operators. However, Mdm K was working about 10m away, packing the finished products into boxes. Environmental monitoring confirmed low levels of TDI (about 0.006mg/m3) at her workstation.

Peak expiratory flow rate (PEFR) monitoring (3 hourly during waking hours, including periods at work and at home) supported the diagnosis of occupational asthma (Fig 1). A bronchial provocation test confirmed that this was due to TDI (Fig 2).

Case 2

Mdm A worked in a similar job as Case 1 but in a different foam factory. She started having cough and episodes of breathlessness and wheezing about 1 3/4 years after joining the factory. She had no past history of asthma. Her symptoms usually occurred 3-4 hours after starting work and again in the early hours of the morning. She consulted many doctors for 6 months with no improvement. Eventually she was referred to a chest physician. Rhonchi were detected in both lungs. PEFR monitoring (Fig 3) and environmental monitoring results showing levels of TDI ranging from 0.006-0.014 mg/m^3 at her workstation supported the diagnosis of occupational asthma due to TDI.

Table I
Summary of the 9 cases of occupational asthma due to isocyanates

Case	Age	Industry	Agent	Latency[1]	Type of Reaction[2]	Atopy[3]	Bronchial hyperreactivity[4]
1. Mdm K	52	foam manufacture	TDI	1 1/2 yrs	immediate (< 1 hour)	+ve	+ve
2. Mdm A	37	foam manufacrture	TDI	1 3/4 yrs	delayed	-ve	+ve
3. Mr C	44	foam manufacture	TDI	2 days	immediate	+ve	-ve
4. Mr P	18	foam manufacture	TDI	2 days	delayed	-ve	ND*
5. Mr T	40	foam manufacture	TDI	2 weeks	immediate	+ve	-ve
6. Mr W	40	spray painting of varnish	Polyisocyanate	2 months	delayed	+ve	ND
7. Mr L	65	spray painting of varnish	TDI	2 days	immediate	ND	ND
8. Mr N	21	insulation of refrigerators	MDI	1 year	immediate	ND	ND
9. Mr H	29	fan belt manufacture	MDI Polyisocyanate	3 months	delayed	+ve	+ve

* Not done
1 Duration from first exposure to Isocyanate to onset of asthmatic symptoms (days, months, years)
2 Time between onset of asthmatic symptoms and challenge or exposure (minutes, hours)
3 Positive prick test to at least one common environmental allergen (Bencard test)
4 Fall of FEV1 > 20% on histamine inhalation challenge testing

Fig 1
Serial PEFR record of Mdm K who was exposed to TDI in her working environment. Increased diurnal variation and fall in the minimum PEFR was seen during periods at work (shaded).

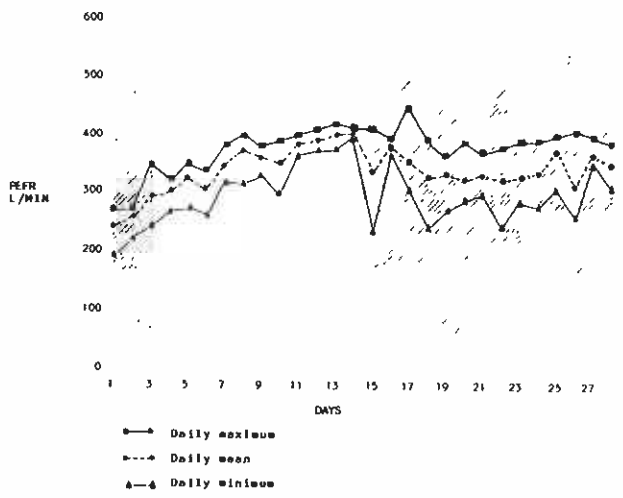


Fig 2
Mdm K's challenge test to TDI. Within 5 minutes of exposure to TDI, her FEV_1 fell by about 50% from her baseline of 2.0 l. This was an immediate type of reaction.

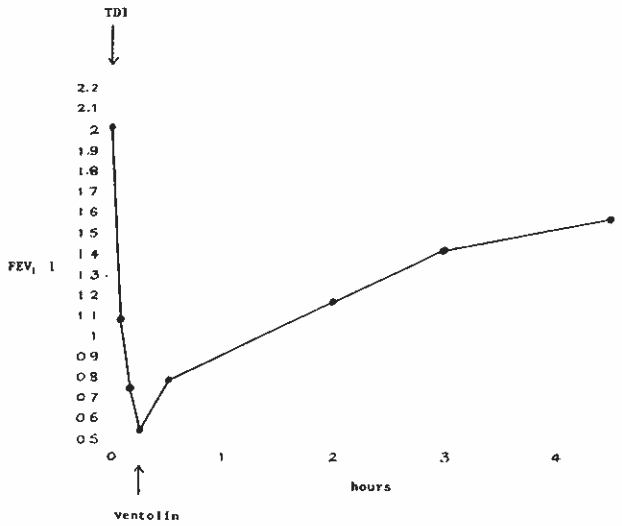
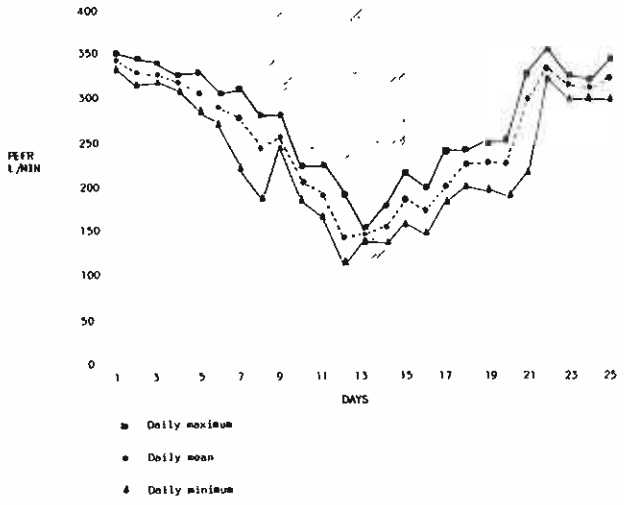


Fig 3
Serial PEFR record of Mdm A who was exposed to TDI in her working environment. Deterioration during period at work (shaded) and improvement during period at home (unshaded) was clearly seen.



Case 3
Mr C was admitted to hospital for acute breathlessness. He had no past history of asthma. Crepitations and rhonchi were detected in both lungs on auscultation. The initial diagnosis was pulmonary oedema. Chest X-ray showed some haziness in the bases. Lung function testing was not carried out.

The occupational history revealed that he had just started work in a foam mattress factory and was directly handling TDI. By the third day he was having an irritating cough. He was treated by a general practitioner and rested at home for 2 days. Within an hour of returning to work (re-exposure to TDI) after his medical leave he developed a cough and breathlessness resulting in his admission to hospital. Environmental measurements confirmed high levels of TDI (above the threshold limit value of 0.04mg/m^3) at the mixing station. Mr C resigned from the factory.

With the occupational history the diagnosis was revised to that of occupational asthma and pneumonitis from TDI. A follow-up one month later showed that he was symptom free since leaving the factory.

Case 4
Mr P was admitted to hospital for acute onset of cough and breathlessness. He had no past history of asthma. The initial diagnosis was extrinsic allergic alveolitis. Both crepitations and rhonchi were heard in the lungs on auscultation. Chest X-ray showed slight haziness in the bases. Blood gas analysis on the day of admission showed a pO_2 of 55.9 mmHg, pCO_2 of 42.0 mmHg and pH of 7.364. Lung Function testing on the third day of admission showed: FEV_1=2.92 l (predicted = 3.80 l), FVC of 4.25 l (predicted = 4.25 l), FEV_1/FVC = 68%, DL_{CO} = 10.34 mmol/min/mmHg (predicted = 11.96 mmol/min/mmHg).

The occupational history revealed that he had just started work in the mixing section of a foam mattress factory (same factory as Case 2) one day before admission. He was directly exposed to TDI vapour at work.

The history and clinical features were consistent with the diagnosis of occupational asthma from TDI exposure.

Case 5
Mr T was admitted to hospital for an acute asthmatic attack. He had no past history of asthma. Rhonchi were detected in both lungs. PEFR on the day of admission was 210 l/min improving to 310 l/min on the 3rd day of admission. Ten days later, his PEFR was 430 l/min. On the 4th day of admission, FEV_1 = 1.56 l (predicted = 3.09 l), post bronchodilator FEV_1 = 1.75 l; FVC =2.86 l (predicted = 3.24 l), post-bronchodilator FVC = 3.56l;FEV_1/FVC = 54%. Chest X-ray was normal.

He had been working in a foam matress factory (same factory as Case 3) for the past 2 months. Two weeks after starting work he already had some symptoms of cough with sputum. He returned to work with TDI one week after discharge from hospital. The next day (after re-exposure) he developed symptoms of cough and breathlessness relieved by the use of the ventolin inhaler. After that he was transferred to work as a lorry driver with improvement of symptoms.

Case 6
Mr W complained of cough with sputum and chest tightness after working for 2 months as a spray painter in a factory making parquet floor tiles. The varnish that he sprayed was found to contain polyisocyanates. During spraying the isocyanate-in-air concentration was 0.075 mg/m^3. His symptoms improved on days away from work. Clinically his lungs were clear. However lung function testing showed an obstructive pattern: FEV_1=1.92 1,FVC = 3. 16 l, FEV_1 /FVC = 60.8%. His PEFR fell from a baseline of 475 l/min to 190 l/min about four hours after exposure to isocyanate at his workplace. He had no past history of asthma.

Case 7
Mr L was admitted to hospital for acute asthma two days after starting work in a furniture factory spraying lacquer containing TDI. Bilateral rhonchi were heard in his lungs. On the third day of admission his lung function was as follows: FEV_1 = 0.93 l (predicted = 2.49 l) post bronchodilator FEV_1 =1.52 l, FVC = 1.61 l (predicted = 3.12 l) post bronchodilator FVC = 2.69 l, FEV_1/FVC = 57.8%.

He had no past history of asthma and had no further attacks after leaving the factory.

Case 8
Mr N complained of cough, breathlessness, wheeze and chest pain about one year after starting work in the foaming section of a factory making marine refrigerators. His symptoms improved on days away from work. He had no past history of asthma. Rhonchi were present in both lungs.

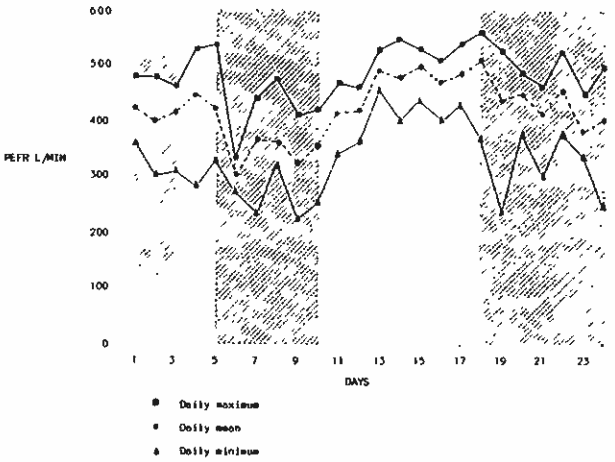
The foam was used for insulation purposes and MDI was injected together with other chemicals into a mould to make the foam. PEFR carried out on one day during the process showed a fall from 335 l/min (baseline) to 265 l/min three hours later (a fall of 29%). The air concentrations of MDI ranged from 0.006-0.014 mg/m^3.

Case 9

Mr H developed symptoms of cough, breathlessness, wheeze and chest tightness about 3 months after starting work in a factory manufacturing rubber fan belting. Rhonchi were present in both lungs. He had no past history of asthma. MDI and polyisocyanates were used in the process. Levels of isocyanate-in-air of about 0.01 mg/m^3 were detected. No other known asthma causing agents were detected. PEFR monitoring (Fig 4) was consistent with the diagnosis of occupational asthma.

Fig 4

Serial PEFR record of Mr H. Improvement during periods at home (unshaded) and deterioration during periods at work (shaded) was demonstrated. He was exposed to MDI and polyisocyanates in his working environment



DISCUSSION

In all the cases the work-relatedness of the asthma was evident from the history and/or the PEFR recordings. None had a past history of asthma. One had a challenge test to TDI. Workplace visits confirmed the presence of isocyanate exposure in all cases. In the absence of other agents known to cause asthma it was reasonable to attribute the work-related asthma to isocyanate exposure.

The importance of the occupational history is illustrated in the above cases. Without a proper occupational history and the knowledge that isocyanates can cause asthma, many of the cases would have just been treated as adult onset asthma. On return to their work their symptoms would recur. Their symptoms may progressively get worse (as in Case 2) or they may simply resign and work elsewhere. Case 3 was initially diagnosed as pulmonary oedema and Case 4 as extrinsic allergic alveolitis. However TDI is a well established cause of asthma and pneumonitis[5,11,12]. With the occupational history and the overall clinical picture the diagnosis was revised to TDI induced asthma and pneumonitis. It is probable that many cases of occupational asthma are not recognised.

It is interesting that the latent period (between first exposure and onset of symptoms) can range from 2 days to 1 3/4 years. The mean latent period for isocyanate workers has been reported as 2 years[13]. Cases 1 and 2 were exposed to lower levels of TDI as they were not directly handling TDI. Their latent period was 1 1/2 and 1 3/4 years respectively. On the other hand Cases 3,4,5 and 7 were all directly exposed to higher levels of TDI. Their latent period ranged from 2 days to 2 weeks. Whether latent period is related to exposure levels requires further investigation. In general, TDI is more potent as an asthma inducer compared to MDI or polyisocyanates. This may be because of its higher volatility[3].

While none of the cases had a past history of asthma, five out of seven who had skin prick testing to common environmental allergens tested posititve to at least one allergen. This gives a prevalence rate of 71% for atopy. It has been reported that atopy is not over-represented among cases of isocyanate asthma[1,3]. Assuming a prevalence rate of 30% - 50% for atopics in the general population[14] there appears to be a slight over-representation of atopics among our cases.

Five of the cases had histamine inhalation challenge testing done and two (40%) did not show bronchial hyperreactivity. Some patients with TDI-induced asthma have been reported to have normal brochial responsiveness[1,6]. The mechanism for TDI-induced asthma has not been established although various theories have suggested including immunological and pharmacological[3,4].

Cases 1 and 2 illustrate that very low levels of isocyanate exposure can induce asthma. Patients with asthma caused by TDI may show significant asthmatic responses on exposure to less than 0.008 mg/m^3 [16]. It has been suggested that once individuals are sensitised to TDI, low concentrations well below the current occupational exposure limits, can induce asthma [5].

Both immediate and delayed reactions were observed in our cases. This has also been the experience of others[1,3]. Asthmatic symptoms developing more than an hour after exposure are considered delayed reactions. Four (44.4%) out of our nine cases had delayed reactions (Cases 2,4 6 and 9). All had their symptoms about two to four hours after exposure to isocyanates while still at work. In addition, Cases 2 and 9 also had symptoms at night. This may suggest dual reactions. It is thus possible for asthmatic symptoms to occur at home (ie. at night or in the late evening) and still be caused by an agent in the working environment.

Four of our cases (Cases 1,2,6 and 8) were followed up one year after the diagnosis was made. Cases 2 and 6 were free from symptoms. Cases 1 and 8 still had occasional episodes of breathlessness and cough (once a month). All had already ceased exposure to isocyanates. The other cases would also be followed up. Studies concerning the long-term follow up of subjects with isocyanate-asthma, report that a significant proportion of subjects (60-80%) who had left the workplace continued to have respiratory symptoms and bronchial hyperreactivity[17,18]. It has been suggested that the development of chronic symptomatic asthma seems particularly liable to occur in those with longer duration of symptomatic exposure[19]. Fatal asthma in a subject sensitised to TDI has also been reported[20]. It is therefore important that cases of occupational asthma be detected early and advice given for them to be permanently transferred from further exposure to the causative agent.

CONCLUSION

Occupational asthma due to isocyanates is not uncommon. It is important to take the occupational history in a patient with asthma. Early diagnosis and removal from exposure could result in a better prognosis for the patient.

REFERENCES

1. Bernstein IL: Isocyanate-Induced Pulmonary Diseases : a current perspective. J Allergy Clin Immunol 1982; 70: 24-31.
2. Seaton A: Occupational Asthma. In : Morgan KC, Seaton A. eds. Occupational Lung Diseases. Philadelphia : WB Saunders Co, 1975: 260-1.
3. Hagmar L, Nielson J, Skerfving S; Clinical Features and Epidemiology of Occupational Obstructive Respiratory Disease Caused by Small Molecular Weight Organic Chemicals. Karger, Basel Monogr. Allergy 1987; 21: 42-58.
4. Mapp CE, Boschetto P, Dal Vecchio L, Maestrelli P, Fabbri LM: Occupational asthma due to isocyanates. Eur Respir J 1988; 1: 273-9.
5. Environmental Health Criteria 75. Toluene Diisocyanates. IPCS International Programme on Chemical Safety, World Health Organisation, Geneva 1987: 44-56.
6. Tanser AR, Bourke MP, Blandford AG: Isocyanate asthma: respiratory symptoms caused by diphenyl-methane di-isocyanate. Thorax 1973; 28: 596-600.
7. Malo JL, Ouimet G,Cartier A, Levitz D, Zeiss CR: Combined alveolitis and asthma due to hexamethylene diisocyanate (HDI) with demonstration of crossed respiratory and immunologic reactivities to MDI. J Allergy Clin Immunol 1983; 72:413.
8. Belin L, Hjortsberg U, Wass U: Life-threatening Pulmonary Reaction from Car Paint Containing Pre-polymerised isocyanate. Scand J Work Environ Health 1981; 7:310-1.
9. Nielsen J, Sango C, Winroth G, Hallberg T, Skerfving S: Systemic Reactions Associated with Polyisocyanate Exposure. Scand J Work Environ Health 1985; 11:51-4.
10. Innocenti A, Cirla AM, Pisati G,Mariano A: Cross-Reaction between Aromatic Isocyanates (TDI and MDI): A Specific Bronchial Provocation Test Study. Clin Allergy 1988; 18: 323-9.
11. Charles J, Bernstein A, Jones B, et al: Hypersensitivity Pneumonitis after Exposure to Isocyanates. Thorax 1976; 31: 126-37.
12. Bascom R, Kennedy TP, Levitz D, Zeiss R: Specific Bronchoalveolar lavage IgG Antibody in Hypersensitivity Pneumonitis from MDI. Am Rev Respir Dis 1985; 131: 463-5.
13. Burge PS: Could You be Overlooking Occupational Asthma? J Respir Dis 1982; 3: 97-112.
14. Venables KM: Epidemiology and the Prevention of Occupational Asthma. Br J Ind Med 1984; 44:73-5.
15. Weill H, Butcher BR, Diem J, et al: Respiratory and Immunologic Evaluation of Isocyanate Exposure in a New Manufacturing Plant. Final Report. DHSS (NIOSH) 1981: public No. 81-25.
16. O'Brien IM, Newman Taylor AJ, Burge PS, Harries MG, Fawcett IW, Pepys J: Toluene di-isocyanate-induced asthma II. Inhalation Challenge tests and bronchial reactivity studies. Clin Allergy 1979; 9: 7-15.
17. Paggiaro PL, Loi AM, Rossi O, et al: Followup Study of Patients with Respiratory Disease due to TDI. Clin Allergy 1984: 14; 463-9.
18. Lozewiez S, Assoufi BK, Hawkins R, Newman Taylor AJ: Outcome of Asthma Induced by Isocyanates. Br J Dis Chest 1987; 81: 14-22.
19. Newman Taylor AJ: Occupational Asthma. Postgrad Med J 1988; 64: 505-10.
20. Fabbri LM, Danieli D, Crescioli S, et al. Fatal Asthma in a Subject Sensitised to TDI. Am Rev Respir Dis 1988; 137: 1494: 8.