Impairment in Workers With Isocyanate-Induced Occupational Asthma and Removed From Exposure in the Province of Québec Between 1985 and 2002

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Objective: *The objective of this project was to assess both the outcome for patients diagnosed with proven isocyanate-induced occupational asthma (IIOA) by specific inhalation challenge (SIC) and the functional impairment, 2 years after cessation of exposure to isocyanates, using the compensation insurance scale proposed in the province of Quebec.* ***Methods:*** *We used a retrospective cohort of 233 patients diagnosed in the province of Quebec between 1985 and 2002 and randomly chose 105 of those patients. We kept 89 subjects with complete data at T_0 (the time of diagnosis) and 79 were reevaluated at T_2, approximately 2 years after their removal from exposure, for final impairment–disability assessment. At each evaluation (T_0 and T_2), a clinical examination and lung function tests, including spirometry and methacholine challenge, were performed.* ***Results:*** *At T_2, 79 of 89 patients were reassessed (89%). The remaining patients were lost to follow up (8) or too unstable to be reassessed for final impairment–disability settlement (2). No statistical difference was observed for spirometry data and antiasthmatic medication use between T_0 and T_2 ($P = 0.11$). At T_2, 73% of patients were still using short-acting β2 agonists and 39% inhaled glucocorticoids. A forced expiratory volume in 1 second variation of ±10% from T_0 to T_2 occurred in 31 subjects (40%). Forced expiratory volume in 1 second worsened in 14 (18%), remained significantly unchanged in 51 (64%), and improved in 14 (18%). Nonspecific bronchial hyperresponsiveness (BHR) improved in significantly in 19 (24%); the others remained unchanged. Both were not associated with smoking status ($P > 0.05$). Nonspecific BHR was normalized in nine of 79 (11%) patients. Clinical remission occurred in only four (5%) subjects. The mean impairment–disability score was 21% ± 13% at 2 years according to the scale used by the Workers' Compensation Board.* ***Conclusions:*** *These results show the generally poor medical outcome of IIOA and suggest the importance of early detection and withdrawal of the workers from exposure to isocyanates. They also emphasize the need for medical surveillance program and adequate treatment of patients with IIOA.* (J Occup Environ Med. *2006;48:1093–1098*)

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Isocyanates are, with flour, the most frequent cause of occupational asthma (OA) in several countries, including Canada (Quebec and Ontario), the United Kingdom, and the United States.[1–5] Isocyanates are low-molecular-weight chemicals used in the manufacturing of polyurethane forms, varnishes, paints, and plastics. Isocyanate-induced occupational asthma (IIOA) has been reported among workers exposed to toluene diisocyanate (TDI), methylene diphenyldiisocyanate (MDI), hexamethylene diisocyanate (HDI), isophorone diisocyanate (IPDI), and naphthalene diisocyanate (NDI). Because the treatment of choice for IIOA is to remove the workers from exposure to the causal agent, the resulting number of people who may be required to change jobs and the ensuing economic consequences for society are of major significance.[6]

Follow-up studies of workers with immunologic OA, ie, asthma caused by sensitization to an agent after a latency period, have shown that avoidance of exposure to the causal agent results in significant improvement of asthma symptoms, airway obstruction, and nonspecific bronchial hyperresponsiveness (NS-BHR). Nonetheless, removal from exposure does not generally lead to complete recovery from asthma. Numerous studies have been published on the prognosis of OA.[7–22]

For prognosis specific to IIOA, a poor outcome of asthma has been as-

sociated with baseline bronchial hyperreactivity and disturbance of ventilatory function.[11,12] Duration of exposure to isocyanate before diagnosis is negatively related to prognosis.[9,10,12] Paggiaro reported persistence of NSBHR in 10 of 16 subjects (62.5%) between 24 and 60 months after the cessation of exposure.[13] Pirila had published the clinical outcome of a large cohort of workers with HDI and TDI occupational asthma.[22] The study was carried out on average 10 years after the diagnosis. According to the questionnaire study done in 213 patients, 80% still felt symptoms of asthma and used medication at the time of the follow up. In that cohort, factors reported to change the prognosis were the presence of immunoglobulin E (IgE) antibodies, probably not in relation to the mechanism of the disease, but probably more in relation to the fact that those patients had a shorter duration of exposure because of an earlier apparition of symptoms compared with the patients with negative IgE antibodies. Patients with HDI-induced asthma had better outcome than those with TDI- and MDI-induced asthma. Atopy, type of reaction to the challenge test, and duration of exposure to isocyanate before the diagnosis were not related to better prognosis in that study.

Impairment resulting from asthma can be quantified using scales that incorporate information on the degree of airflow limitation, the level of NSBHR, and medications required to control symptoms as recommended by the American Medical Association.[23] In Quebec, the compensation program provided by the Commission de la santé et sécurité du travail (CSST) allows for financial support to the workers who are completely removed from exposure to isocyanates. On diagnosis, an initial impairment of 3% is given to all workers for sensitization, whereas a second assessment of impairment is carried out 2 years after the diagnosis.

Assessment of impairment is carried out 2 years after diagnosis, because previous studies have shown that improvement of the functional status reaches a plateau 2 years after cessation of exposure. This has been shown in workers exposed to snow crab.[18] However, subsequent studies have shown that NSBHR can further improve 5 years and more after cessation of exposure.[23]

The objective of this project was to assess both the outcome for patients diagnosed with proven IIOA by specific inhalation challenge (SIC) and the functional impairment 2 years after cessation of exposure to isocyanates using the compensation insurance scale proposed in the province of Quebec.

Subjects and Methods

This is a retrospective cohort study. Patients included in that cohort were those diagnosed with IIOA between July 1985 and December 2002 and recognized by the Workers' Compensation Board (WCB) with a temporary attributed impairment–disability score (IDS) of 3% due to sensitization to isocyanates. A total of 233 patients were diagnosed in the province of Quebec between these years, and we randomly chose by computer-assist randomization 105 of those patients who were assessed at T_0 (time of diagnosis). We had complete data on 89 of them that we kept in the cohort. 79 were reassessed at T_2, approximately 2 years after their removal from exposure for final impairment–disability assessment. At each evaluation, a clinical examination and lung function tests, including spirometry and histamine or methacholine challenges, were performed. Skin testing was performed by the prick method using a battery of ubiquitous inhalants. Histamine hydrochloride (1 mg/mL) was used as a positive control. Skin reactions of 3 mm or larger were considered positive in the presence of a negative reaction to the diluent. Two different definitions were used for atopy: 1) one or more positive skin prick reactions after testing with a battery of common environmental allergens, and 2) previous manifestations of eczema, atopic dermatitis, hayfever, or other allergic rhinitis, referred to here as atopic history. All these informations were available in patient records in the WCB database that we use for this study.

Variables

Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, histamine or methacholine concentrations causing a fall of 20% in FEV_1 (PC_{20}), medication to control asthma, and IDS at T_0 and T_2 were considered. IDS estimation is based on three factors according to the scales previously established.[24]: air caliber, airway responsiveness, and the need for medication to adequately control asthma. That scale is represented in Table 1. The duration of exposure, the latency period necessary for developing symptoms, and the duration of exposure after the onset of symptoms were assessed.

Data Collection

We collected data according to established standard procedures from the database of the WCB (CSST in Québec), which included the subjects' medical reports. These reports present data on occupational and asthma history, smoking status, asthma medication, personal and family health history, physical examinations, lung function tests, chest x-rays, IDS, and conclusions.

Statistical Methods

We compared the clinical characteristics from the time of diagnosis (T_0) to 2 years thereafter (T_2). A FEV_1 variation of $\pm$ 10% from T_0 to T_2 was considered significant.[25,26] An improvement in NSBHR was significant if PC_{20} at T_2 was 3.2 times greater than PC_{20} at T_0.[27] A NSBHR was considered normalized if, at T_2, PC_{20} >16 mg/mL. Clinical remission occurred when PC_{20} >16 mg/mL without the use of antiasthmatic medication susceptible of influencing NSBHR or needed to control asthma, except for the occasional use of short-

TABLE 1
Functional Class and Functional Impairment Scale in Occupational Asthma in the Province of Quebec

Class	Bronchial Obstruction	Bronchial Reactivity	Medication Needs	IDS
1	0	0	No	0
2	0	1	No	5
	0	1	SBA PRN	8
	0	1	SBA or LBA REG	10
	0	2	No	10
	0	2	SBA PRN or REG	13
	0	3	SBA PRN or REG	15
3	1	1	SBA PRN or REG	18
	1	2	SBA PRN or REG	20
	1	3	SBA PRN or REG	25
4	2	1–2	SBA PRN or REG	28
	2	3	SBA PRN or REG	33
5	3	1–2	SBA PRN or REG	50
	3	3	SBA PRN or REG	60
6	4	1–2–3	Oral steroid	100

Bronchial obstruction: 0 = FEV_1 and/or FEV_1/FVC >85%; 1 = FEV_1 and/or FEV_1/FVC = 71% to 85%; 2 = FEV_1 and/or FEV_1/FVC = 56% to 70%; 3 = FEV_1 and/or FEV_1/FVC = 40% to 55%; 4 = FEV_1 and/or FEV_1/FVC <40%.

Hyperreactivity level: 0 = PC_{20} >16 mg/mL; 1 = PC_{20} = 2–16 mg/mL; 2 = PC_{20} = 0.25–2 mg/mL; 3 = PC_{20} <0.25 mg/mL.

Immunologic sensitization: IDS = 3%.

Inhaled glucocorticoids = 3%.

We set the IDS in accordance with the scale and we added 3% for sensitization to a specific agent and 3% if regular inhaled glucocorticoids are used.

IDS indicates impairment–disability score; SBA, short β2-agonist; PRN, as needed; LBA, long β2-agonist; REG, regularly; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

TABLE 2
Sociodemographics and Duration (isocyanate exposure, latency period, symptoms) at Diagnosis

	$\bar{x} \pm \sigma$	No. (%)
Sex (female/male)	—	80/9
Age (yr)	45 ± 11	89
Smoking		
Never	—	32 (36%)
Current	—	17 (19%)
Previous	—	40 (45%)
Durations (mo)		
Exposure	155 ± 148	89
Latency	94 ± 112	89
Symptoms	61 ± 66	89
Isocyanates		
HDI	—	27 (35%)
MDI	—	13 (17%)
TDI	—	14 (18%)
IPDI	—	1 (1%)
HDI + MDI	—	1 (1%)
HDI + TDI	—	1 (1%)
HDI + IPDI	—	3 (4%)
MDI + TDI	—	1 (1%)
Not identified	—	28 (22%)

HDI indicates hexamethylene diisocyanate; MDI, methylene diphenyldiisocyanate; TDI, toluene diisocyanate; IPDI, isophorone diisocyanate.

acting β2-adrenergic. We tested categorical data using Fisher exact test or Pearson χ^2 (with Yates correction for continuity) and continuous variables (paired, unpaired data) using the Student *t* test. We used Mann-Whitney *U* and Wilcoxon signed rank tests for paired and unpaired nonparametric data, respectively. We assessed the correlations using Pearson or Spearman correlation coefficients. Two-sided *P* values of less than 0.05 were considered to indicate a statistically significant difference. Data were processed using SPSS package (version 10.0).

Ethics

The Ethics Committee of Hôpital du Sacré-Cœur de Montréal approved this study. The Commission d'Accès à l'Information (CAI) of Quebec, that allows access to and protects information on privacy, approved access to the patient medical reports from the CSST.

Results

Between July 1985 and November 2000, 233 diisocyanate-induced asthma subjects were assessed and recognized for IIOA by the WCB in the Province of Quebec (CSST); 105 of them were randomly selected for our study. Of those 105 cases, we kept 89 subjects for our study, 10 were not reassessed by the CSST after 2 years (eight were lost at follow up and two undertreated for their asthma so not stable enough to be reassessed). It would have been interesting to know the evolution of the subjects lost to follow up; generally those are the ones with the better prognosis who work another job and who are not interested in lost time from work and coming in for their revaluation. Therefore, we have complete results on 79 patients. In 97% of the cases, the diagnosis was proven by SIC. Among 86 IIOA cases out of 89 patients at the time of diagnosis (T_0), 49% worked spray painting in body shops, 19% in manufacturing, 8% in construction, 8% in chemical industries, 4% in communications, 2% in furnishing, 2% in aviation, and 4% in the rubber, 2% in the leather, and 2% in the textile industries. Among 89 IIOA cases with an average age of 45 years (9 female, 80 male), 32 (36%) were nonsmokers, 17 (19%) were current smokers, and 40 (45%) were former smokers (Table 2). Skin prick tests to a battery of 20 environmental allergens were performed in 52% (46) of the cases, and 46 (100%) were positive to at least one allergen. Atopic history of earlier conjunctivitis, dermatitis, eczema, hayfever, or rhinoconjunctivitis was reported by 14%. The total duration of exposure, the latency period necessary for acquiring sensitization, and the duration of

exposure after the onset of symptoms averaged 155, 94, and 61 months, respectively. After the diagnosis of IIOA, patients were advised to avoid isocyanate exposure and were granted compensation. Isocyanates agents that had caused asthma were HDI (35%), MDI (17%), TDI (18%), IPDI (1%), HDI + MDI (1%), HDI + TDI (1%), HDI + IPDI (4%), and MDI + TDI (1%) for (22%) the type of isocyanate was not mentioned (Table 2).

At T_2, for 79 patients, no statistical difference was observed for spirometry data and antiasthmatic medication use between T_0 and T_2 ($P = 0.11$). At T_2, 73% of patients were still using short-acting β2 agonist and 39% inhaled glucocorticoids (Table 3). A FEV_1 variation of ± 10% from T_0 to T_2 occurred in 31 subjects (40%). FEV_1 worsened in 14 (18%), remained significantly unchanged in 51 (64%), and improved in 14 (18%). NSBHR improved significantly in 19 (24%); the others remained unchanged. Both were not associated with smoking status ($P > 0.05$). NSBHR was normalized in nine of 79 (11%) patients. Clinical remission from our previous definition occurred in only four (5%) subjects. The mean IDS was 21% ± 13% at 2 years according to the scale used by the WCB (Table 3).

Discussion

We investigated the outcomes of the 89 workers of whom 97% were diagnosed with IIOA. Legislation in the province of Quebec permits workers diagnosed with IIOA to be financially compensated once removed from exposure to isocyanates. Our results show that FEV_1 significantly increased in 36% of the workers. NSBHR improved significantly in 24%. NSBHR was normalized in 11%. Clinical remission which means normalization of bronchial reactivity and no need for any antiinflammatory treatment occurred in only 5%. Antiasthmatic medication use did not differ between T_0 and T_2 ($P = 0.11$). Seventy-three percent of patients still need β2 agonists and 36% need inhaled glucocorticoids 2 years after having been removed from the exposure. This indicates that many patients still had symptoms 2 years after a diagnosis of IIOA. In a published series by Piirila on 245 cases of IIOA, 82% still experienced asthma symptoms and used asthma medication after an average follow up of 10 years.[22] Reassessment was carried out by a questionnaire on 154 patients and by a questionnaire plus a functional evaluation on the remaining 91 patients. The average duration of symptoms was 82 ± 71 months, which is comparable to our series. In the series of

TABLE 3
Patient Clinical Characteristics at Isocyanate-Induced Occupational Asthma Diagnosis (T0) and 2 Yr Later (T2)

	T_0			T_2			
	$\bar{x} \pm \sigma$	Median	No.	$\bar{x} \pm \sigma$	Median	No. (%)	*P*
Atopic history							
Eczema	—	—	1	—	—	—	—
Conjunctivitis	—	—	2	—	—	—	—
Rhinitis	—	—	7	—	—	—	—
Rhinoconjunctivitis	—	—	2	—	—	—	—
Urticaria	—	—	1	—	—	—	—
Atopy*			46/46				
One+	—	—	100%	—	—	—	—
Spirometry							
FEV_1†	82% ± 19%	—	89	84% ± 21%	—	79	0.99
FVC†	100% ± 18%	—	89	99% ± 18%	—	79	0.29
FEV_1/FVC†	82% ± 12%	—	89	82% ± 13%	—	79	0.86
PC_{20}	—	1.8‡	75	—	1.50‡	63	0.78
Asthmatic medication							
β2-adrenergic bronchodilators							
Short-acting	—	—	66	—	—	58	
Long-acting	—	—	7	—	—	12	
Theophylline	—	—	6	—	—	2	
Anticholinergic bronchodilators	—	—	2	—	—	1	
Corticosteroids							0.11
Inhaled	—	—	38	—	—	31	
Oral	—	—	1	—	—	2	
Antileukotrienes	—	—	0	—	—	5	
β2-adrenergic + corticosteroids	—	—	1	—	—	3	
Impairment–disability score	3% ± 0%	—	89	21% ± 13%	—	79	<0.01

*Positive skin prick reactions.
†As a percentage of the predicted values.
‡Median.
FEV_1 indicates forced expiratory volume in 1 second; FVC indicates forced vital capacity.

Padoan, 60% of the patients removed for 10+ years reported asthmatic symptoms and 60% of workers needed therapy with bronchodilators, whereas 20% used inhaled glucocorticoids.[28] The program's facilities of the province of Quebec suggested that the prognosis would be better than the one usually reported in the literature. Unfortunately, our results are no better than those reported. We must realize that the total duration of exposure, the latency period necessary for acquiring sensitization, and the duration of exposure after the onset of symptoms was very lengthy in our patients. They averaged 155, 94, and 61 months, respectively. So, patients had a major exposure period after respiratory symptoms had appeared, indicating a related poor prognosis. However, in contrary to the two previous series on IIOA, our patients were reassessed just 2 years after their removal from exposure. They would have had less severe impairment if the reassessment had been done 5 to 10 years after. BHR (CP_{20}) and disturbance of ventilatory function (FEV_1) at T_0 are significantly and negatively correlated to the prognosis, respectively ($r = -0.57$, $P = 0.01$ and $r = -0.59$, $P = 0.01$). These results are in accordance with the previous results.[11,12] The presence of specific IgE antibodies to isocyanates was found to be associated with a favorable prognosis. We did not measure the specific IgE in this study. The relationship between isocyanate exposure levels and the risk of sensitization is very well known.[29] However, there are few publications on the relationship between prognosis and intensity or cumulative exposure,[30] and we have no idea of the level exposure of those workers in that cohort study. Our cases of IIOA were almost all proven by SIC, confirming the immunologically mediated asthma mechanism for 87 of 89 patients. Others series could have included patients with underlying bronchial hyperresponsiveness without immunologic IIOA, therefore generating heterogeneity in prognosis.[31,32]

Conclusion

These results show the persistence of asthma in the majority of subjects with IIOA 2 years after cessation of exposure (only 5% of clinical remission in our cohort) That suggests the importance of early detection and withdrawal of the worker from exposure to isocyanates. They also emphasize the need for medical surveillance and adequate treatment of patients with IIOA. We are currently conducting a surveillance program in the province of Quebec for workers exposed to isocyanates and projecting improvement of the prognosis through early detection.

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