

Importance of specific inhalation challenge in the diagnosis of occupational asthma induced by quaternary ammonium compounds

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Clinical Implications

- Specific inhalation challenges appear necessary to confirm the diagnosis of occupational asthma to quaternary ammonium compounds.

TO THE EDITOR:

Epidemiological studies have demonstrated a relationship between exposure to quaternary ammonium compounds (QACs) and asthma, particularly among health care workers and domestic cleaners, who are the first and second most frequently reported occupations among all cases of work-related asthma according to the American SENSOR Program, SWORD (Surveillance of Work-related and Occupational Respiratory Disease) in the United Kingdom, and ONAP (Observatoire National de l'Asthme Professionnel) in France.^{1,2} These workers are exposed to cleaning products containing both irritants and sensitizers such as cleaning sprays, bleach, terpenes, aldehydes, and ammonia and also QACs. The diagnosis of QAC-induced occupational asthma (OA) is still difficult and specific inhalation challenge (SIC) may help.^{3,4} However, the availability of SIC is limited to a very few centers in the world and reports on inhalation challenges with QACs are scarce in the literature. We assessed whether SIC is useful in the diagnosis of OA induced by QACs.

This study was a retrospective analysis of the records of subjects who were investigated for QAC-related asthma symptoms by an SIC in our center between 2009 and 2012. SICs were completed according to a standardized protocol, and all patients signed an informed consent. On the first day, a control challenge was performed by exposing the subject to saline for a cumulative time of 1 hour to ensure that fluctuations in FEV₁ were less than 15%. On the following day, the patients were challenged, if available, with the pure QAC, suspected of causing their asthma. The products were diluted in cold water at concentrations varying from 0.1% to 1% according to the analysis of occupational exposure and the extent of the asthmatic reaction at work. Patients were exposed in a realistic manner in a 9-m³ chamber at a controlled ventilation rate. A bucket containing 3 L of diluted product was placed in the cabin. Either the patient remained just sitting or the patient washed the cabin table. The duration of exposure was gradually increased (ie, 1, 2, 4, 8, 15, 30 minutes), with 10-minute intervals between each exposure until an immediate bronchial response (15% fall in FEV₁) was obtained or until a cumulative duration of exposure of 1 hour was reached. In the absence of a significant

immediate or late bronchial response (15% fall in FEV₁ during the next hours), nonspecific airway hyperresponsiveness (AHR) to methacholine was measured, 4 hours after the end of the SIC, and compared with the baseline level 1 day before the SIC. A significant increase in postchallenge nonspecific AHR to metacholine (ie, more than 2-fold reduction in postchallenge provocation dose causing a 20% fall in FEV₁) compared with baseline^{4,5} was considered as a positive challenge outcome as recommended by the European Respiratory Society.⁶ Comparisons were performed using the Fisher exact test or the Wilcoxon test. The significance level was set at 5%. All the analyses were performed using R 3.0.2.

Among the 22 challenged patients, 12 (55%) had a positive outcome. The main characteristics of the patients are presented in Table I. There was no significant difference between the characteristics of patients with a positive SIC or a negative SIC in terms of clinical history, functional values, type, and duration of exposure. Although the difference was not significant, patients with a positive SIC were more often atopic (58%), or more frequently had rhinitis (75%) and/or conjunctivitis (42%). None of the patients reported rash during their former occupational exposure. Patients with a positive SIC had higher exhaled nitric oxide values at work than did patients with a negative outcome, but the difference did not reach statistical significance ($P > .05$). The most frequent QAC was didecylmethylammonium chloride (Table II). Most of the patients with a positive outcome presented an immediate bronchial response ($n = 6$ isolated and $n = 1$ dual). The remaining patients with a positive outcome presented a significant increase in their nonspecific AHR 4 hours after the SIC.

In our study, there was no difference between the patients who had a positive SIC to QACs and those in whom it did not elicit a bronchial response. This differs from the results of Vandenplas et al, which showed that those who had a positive SIC to cleaning agents used more short-acting beta-2 agonists and had a more severe basal airway obstruction. Those from Strasbourg had milder asthma than did those from Belgium because, in our group, none was on high doses of inhaled corticosteroids compared with 29% in Vandenplas et al's article. Even if there are slight differences between the 2 studies, our results showed that it is difficult to confirm the diagnosis of QAC-induced OA without performing an SIC. As stated in the recent European recommendations on SICs,⁵ the procedure for conducting them must be standardized as far as possible with at least 1 day of exposure to placebo. As opposed to other groups, we did not undertake a second day of exposure to higher doses of QACs in patients who failed to develop significant changes in FEV₁ or PD₂₀ to increase sensibility of the test. This could explain lower rates of positive outcomes. Moreover, lack of significant differences between our 2 study groups might also be related to the relatively small sample size in each group of patients. The mechanism by which QACs induce asthma is still disputed, and the specificity of a positive inhalation outcome has to our knowledge not been assessed. This point is a potential limitation of our study. It has been shown in the past that the obstruction induced by benzalkonium chloride might be an irritant because of a short duration of action before the onset of asthma symptoms during SIC.⁷ However, in our study, the immediate bronchial response appeared after a mean time of 19 minutes

TABLE I. Patients' characteristics

Characteristic	Positive SIC (n = 12)	Negative SIC* (n = 10)
Sex: M/F	1/11	0/10
Age (y)	48.7 ± 7.5	45.8 ± 9.1
Occupation (n)		
Cleaner	3	2
Nurse	3	0
Nursing assistant	2	3
Laboratory technician	0	1
Dentist	1	1
Dental assistant	1	1
Hospital housekeeper	1	0
Swimming pool employee	0	1
Nursery assistant	1	0
Fish factory worker	0	1
Current and ex-smokers, n (%)	4 (33)	6 (60)
Atopy, n (%)	7 (58)	2 (20)
Mean duration of exposure before onset of asthma at work (mo)	126.2 ± 138.4	101.8 ± 133.7
Median duration of exposure before onset of asthma at work (mo)	96 ± 132.5	48 ± 135
History of conjunctivitis, n (%)	5 (42)	3 (30)
History of rhinitis (%)	9 (75)	5 (50)
Baseline FEV ₁ (% predicted)	100 ± 12.3	97.4 ± 13.8
Baseline FEV ₁ (L)	2966.4 ± 132	3061.9 ± 111
Baseline airway obstruction (FEV ₁ <80%), n (%)	1 (8)	0 (0)
Inhaled corticosteroids, n (%)	5 (42)	3 (30)
Low dose	3 (25)	3 (30)
Medium dose	2 (17)	0 (0)
High dose	0 (0)	0 (0)
Short-acting β ₂ agonists ≥ once a day, n (%)	1 (8)	2 (20)
Out of work exhaled NO (ppb)	23 ± 19	19 ± 4
Work exhaled NO (ppb)	49 ± 64	17 ± 4

F, Female; M, male; NO, nitric oxide; ppb, part per billion.

Data are presented as n (%) or as mean ± SD. Low-dose corticosteroids, ≤500 µg of beclomethasone dipropionate equivalent per day; medium dose, 500 to 1000 µg/d; high dose, ≥1000 µg/d.

*P > .05.

(from 3 to 48 minutes), which corresponds to the median time we observed in 12 positive SICs in bakers, commensurate with the typical IgE-mediated mechanism of OA (19 minutes [6-30]) (personal communication, Mael Bellier 2014). This suggests that QACs might also induce OA through a specific immunologic response—sensitizing mechanism because it has been suggested for other low molecular weight occupational agents (ie, isocyanates).⁸ However, this dichotomy of sensitization versus irritation in the onset of QAC-induced OA remains unclear because both mechanisms may be involved.⁹ Moreover, allergens can also act as irritants, as do pollens that contain pollen-associated lipid mediators. This may be true for high molecular weight in OA because it has been shown that only 50% of the patients who had symptoms in contact with laboratory animals were sensitized.¹⁰

To conclude, SICs to QACs appear necessary to confirm the diagnosis of QAC-induced OA because there are no particular clinical or functional characteristics in patients who developed asthma when exposed to QACs.

TABLE II. SIC characteristics

Characteristic	Positive SIC (n = 12)	Negative SIC (n = 10)
Type of QAC (n)		
Didecyl dimethyl ammonium chloride	9	7
Alkyl dimethyl benzyl ammonium chloride	1	
Didecylmethyl ammonium propionate		1
Benzalkonium chloride	2	1
Bis-aminopropyl-laurylamine and amine oxide		1
Immediate bronchial response (n)	7	NA
Mean fall in FEV ₁ (%)	23.4 ± 5.7	NA
Mean duration of exposure (min)	18.5 ± 14	NA
Median duration of exposure (min)	15 ± 13	NA
Rhinitis (n)*	8	3
Metacholine inhalation test (n)	5	10
Mean maximum fall in FEV ₁ during SIC in patients who underwent a metacholine inhalation test (%)	8.8 ± 2.8	7.9 ± 3.5

NA, Not applicable.

Data are presented as n or as mean or median ± SD.

*P > .05 (Fischer exact test).

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