

Airway Response to Chlorine inhalation (Bleach) Among Cleaning Workers With and Without Bronchial Hyperresponsiveness

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Background Symptoms of obstructive lung disease in domestic cleaning staff have been related to the use of bleach and other irritant cleaning products.

Material and Methods Included in the study were thirteen cleaning employees with work-related asthma-like symptoms, three asthmatic controls and three atopic subjects without bronchial hyperresponsiveness (BHR) who had no exposure to cleaning products. The study protocol consisted of a methacholine test, sputum induction and fraction of exhaled nitric oxide measurement (FENO) both at baseline and 24 hr after a 1-hr inhalation challenge with either placebo or bleach at a concentration of 0.4 ppm of chlorine.

Results The inhalation of the placebo caused no bronchial reactions. Mean maximum fall in FEV₁ during challenge testing with bleach was significantly higher than the values obtained during the placebo challenge. Inhalation challenge with bleach elicited two isolated late asthmatic reactions and one dual asthmatic reaction. Of all the patients who underwent challenge testing with bleach, only one had a ≥ 2 -fold decrease in methacholine PC₂₀ 24 hr after the challenge. No significant correlation was found between maximum fall in FEV₁ and PC₂₀ methacholine. Following challenge testing with bleach, no clinically significant changes in sputum cell counts or FENO were detected.

Conclusions These results suggest that bleach inhalation at a concentration of 0.4 ppm—a concentration below 8-hr permissible occupational exposure level—brings about a substantial decrease in FEV₁ in subjects with and without BHR. Some subjects have a positive challenge response to bleach inhalation. *Am. J. Ind. Med.*

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KEY WORDS: irritant asthma; bronchial hyperresponsiveness; chlorine; cleaner's asthma

Abbreviations: SIC, specific inhalation challenge; OA, occupational asthma; LMW, low molecular weight; HMW, high molecular weight; FENO, fraction of exhaled nitric oxide; Ns, not significant; ppm, parts per million; BHR, bronchial hyperresponsiveness; TLV, threshold limit value.

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INTRODUCTION

The cleaning products used for common janitorial tasks are mixtures of many chemicals. Bleach (sodium hypochlorite) and ammonia are among the most common chemicals used in such products.

Cleaning staff have an increased risk of persistent adult-onset asthma [Karjalainen et al., 2002]. In a study conducted in Spain more than half of the janitorial employees surveyed reported work-related respiratory symptoms; of these individuals, employees who worked in homes were the most likely to report such symptoms [Zock, 2005; Zock et al., 2001]. In other Spanish studies, exposure to bleach and possibly other irritant agents has been associated with lower respiratory tract symptoms on work days and asthma symptoms both in the workplace and at home [Medina-Ramon et al., 2005, 2006].

Rosenman et al. [2003] reviewed the reports published by four U.S. states on work-related asthma associated with cleaning products. A cleaning product was one (or more) of the three suspected agents identified in 236 (12%) of the 1,915 confirmed cases that met the surveillance definition of work-related asthma. Of the products identified, bleach was the most frequent.

Few studies have investigated the short-term effect of challenge testing with bleach on bronchial responsiveness. Medina-Ramon et al. [2006] performed peak expiratory flow (PEF) measurements on domestic cleaning workers with respiratory disorders. Lower respiratory tract symptoms were more common on work days and were predominantly associated with exposure to diluted bleach, degreasing sprays/atomizers and air fresheners. However, associations with upper respiratory tract symptoms and PEF measurements were less apparent.

D'Alessandro et al. [1996] exposed both patients with non-specific bronchial hyperresponsiveness (BHR) and control subjects to 0.4 and 1 ppm of chlorine. After 0.4 ppm chlorine inhalation, there was no significant pulmonary function effect. However, at 1 ppm patients with BHR experienced greater specific airway resistance than normal subjects ($P=0.04$), and the same difference was found in proportional change in FEV1 after 1.0 ppm chlorine as compared with baseline reactivity. These data pointed out that subjects with hyperreactive airways experience an exaggerated airway response to chlorine at 1.0 ppm.

In this article we investigate the effects of bleach inhalation on pulmonary function and inflammatory markers among cleaning staff with and without BHR. We also study asthmatics not employed in cleaning services as well as non-asthmatic patients not exposed to bleach.

METHODS

Subjects

All subjects were recruited at the Fundación Jiménez Díaz Allergy Outpatient Clinic.

Thirteen cleaning employees with asthma-like symptoms related to their occupation were included. All subjects were exposed to bleach, but some entered into contact with other products as well (i.e., ammonia, degreasing agents). All were employed in janitorial services at the time.

These patients were then classified as having BHR if methacholine challenge testing at a concentration <8 mg/mL induced a fall of 20% or more in FEV₁ with respect to baseline values.

Three asthmatic controls with no asthma symptoms related to cleaning products were included in the study. All had positive methacholine tests ($PC_{20} < 8$ mg/mL) and two were atopic. Subjects regarded as asthmatic presented a consistent history and had objective evidence of asthma (as defined by the American Thoracic Society) for at least 6 months. Asthmatic patients had mild persistent disease and were clinically stable. Three patients with no history of asthma and PC_{20} methacholine >16 mg/mL were also included, all of whom were atopic. The subjects' clinical characteristics are shown in Table I.

Study Protocol

On the first day (control day), a full medical and occupational history was completed. Patients who had been receiving inhaled corticosteroids (five cleaning employees and three patients with asthma) discontinued use of these drugs for at least 2 weeks before sputum induction. Before specific inhalation challenges (SICs) commenced, bronchodilators were withdrawn for a period of time equal to the drugs' duration of action. No patient was receiving oral corticosteroids (for at least 6 months prior to the study) or leukotriene receptor antagonists. Spirometry and methacholine challenge testing was performed as described elsewhere [Sastre et al., 2003]. These tests, together with sputum induction and FENO values measurement (NIOX MINO, Aerocrine, Sweden), were carried out at baseline and 24 hr after SIC with either placebo or bleach.

This study was approved by the Fundación Jiménez Díaz Institutional Review Board, and all subjects gave written informed consent to participate in the study.

Bleach Inhalation Challenges

Single-blind SICs were performed in a 7 m³ challenge chamber on separate days. On visit 1, FENO and PC_{20} were

TABLE I. Clinical Characteristics of Study Subjects

Patients #	Age	Atopy	Smoking history	% Predicted FVC	% Predicted FEV ₁	% FEV ₁ /FVC	Time working in cleaning (years)	Latency of RS after work start (years)	Previous treatment
1	27	No	No	82	66.9	70.8	1	0.3	SABA.prn
2	45	No	Yes	89.5	87.3	83.67	14	7	LABA + ICS
3	35	Yes	No	104.1	100.9	83.99	2	1	LABA + ICS
4	48	Yes	No	102	103	92	20	4	LABA + ICS
5	46	Yes	No	98	93	88	12	3	NO
6	46	Yes	No	106.6	101.7	81.79	6	3	SABA
7	29	No	No	97.2	83.6	74.74	4	2	LABA + ICS
8	53	No	No	122	116.00	79.00	8	2	SABA.prn
9	42	Yes	No	101	85.00	72.00	9	6	NO
10	59	Yes	Yes	147	154	87.00	10	7	NO
11	28	No	No	122	116	82.00	5	1	NO
12	41	Yes	No	115	112	83.00	6	3	LABA + ICS
13	33	Yes	No	128	119	80.00	8	2	NO
14	26	No	No	110	100	83			ICS
15	54	Yes	No	132	115	73			LABA + ICS
16	27	Yes	No	106	105	86			LABA + ICS
17	37	Yes	No	103	95	97			SABA.prn
18	30	Yes	No	109	107	84			SABA.prn
19	57	Yes	No	137	127	77			LABA + ICS

SABA, short acting B2; LABA, long acting B2; ICS, inhaled corticosteroids; RS, respiratory symptoms
 Patients 1 – 13 are janitorial workers.

measured, and sputum induction was performed. On visit 2, patients were exposed to a placebo (saline solution) using the same system as the one described for bleach for a total of 60 min. On visit 3, the patient underwent an SIC with commercial bleach (5% sodium hypochlorite). A dose of 30 ml was nebulized using a DeVilbiss 2000® ultrasonic nebulizer (DeVilbiss Healthcare, Somerset, PA) to reach a chlorine concentration of 0.4 ppm. Chlorine concentration was continuously measured with a MDA monitor (model 7100; MDA Scientific, Greenview, IL). During exposure, the subjects were seated and at rest. All exposures were carried out for 60 min, and, throughout the study, temperature and humidity were kept constant at 20°C and 40%, respectively. We chose 0.4 ppm because this concentration is below the recommended 8-hr permissible occupational exposure level of 0.5 ppm for chlorine (1.0 ppm is the recommended 15-min ceiling for short-term occupational exposure to chlorine TLV-STEL, <http://www.osha.gov/SLTC/healthguidelines/chlorine/recognition>). Twenty-four hours later, on visit 3, methacholine inhalation tests, FENO measurement and sputum induction were performed again. Spirometry was performed 5, 10, 20, 30, 40, and 60 min after the inhalation challenge. From that moment, PEF and FEV₁ were measured hourly with a computerized flowmeter (Amos, Viasys, Germany) for 24 hr after the challenge, though sleep time was respected. During the 24-hr follow-up period, a fall in

FEV₁ of 20% or more with respect to baseline levels was considered a positive challenge.

Ad hoc short-term personal exposure measurements of airborne chlorine were taken by simulating the cleaning of a bathroom measuring 9.8 m³. Commercial bleach (5% sodium hypochlorite) was used to clean the toilet bowl, shower, and toilet while the door remained closed. The total duration of the cleaning process was 5 min. On one occasion, cleaning was performed by spraying bleach with a household sprayer and on the second occasion, which took place on a different day, the bleach was poured. In both instances we used a piece of cotton dust cloth to clean the surfaces.

Sputum Induction and Processing and Flow Cytometry of Sputum Cells

The protocol for sputum induction and its analysis by flow cytometry have been described elsewhere [Sastre et al., 2003, 2008]. Analyses were blinded for lab personnel. Normal values for sputum cell counts are described in other reports [Sastre et al., 2008; Fernandez-Nieto et al., 2009].

Data Analysis

Subjects' characteristics were recorded using descriptive statistics and expressed as mean and standard deviation

(SD). Normality was analyzed using the Kolmogorov–Smirnov test. Comparisons of mean values between groups were performed using the Wilcoxon signed-rank test, the Kruskal–Wallis test and the Mann–Whitney *U*-test and ANOVA and unpaired *t*-test with Welch correction or *t*-test for non-parametric data and parametric data, respectively. Differences were considered to be significant when $P \leq 0.05$.

RESULTS

The results of the tests performed on all patients included in the study are shown in Table II.

Specific Inhalation Challenges

A total of 38 SIC were carried out, 19 with a placebo and 19 with bleach. Placebo challenges did not induce any positive reactions. Mean maximum fall in FEV₁ during the placebo challenge was 0.094 ± 0.057 L. SICs elicited two isolated late asthmatic reactions (FEV₁ fall of 33% at 6 hr and 34% at 3 hr from baseline, respectively) as well as one dual asthmatic reaction (FEV₁ fall of 26% at 30 min and 40% at 8 hr from baseline, Fig. 1). Among patients with positive SIC, one had a positive methacholine test at baseline, but 24 hr after SIC, none had a ≥ 2 -fold increase in methacholine PC₂₀. Of all patients challenged with bleach, only one had a ≥ 2 -fold increase in methacholine PC₂₀ 24 hr after SIC. This patient was a janitorial employee with a baseline methacholine PC₂₀ of 5.8 mg/ml. In patients with positive methacholine tests, PC₂₀ before SIC with bleach was significantly higher than it was after SIC ($P = 0.028$).

Mean maximum fall in FEV₁ (in liters) after bleach challenge was 0.346 ± 0.27 L ($P < 0.0001$ in comparison with mean maximum fall of FEV₁ during placebo challenge). No significant changes in FVC were observed after bleach challenge. Patients with positive methacholine tests were observed to have a mean maximum FEV₁ fall after bleach challenge of 0.414 ± 0.284 L, and in subjects with negative methacholine tests, this value was 0.271 ± 0.248 L, n.s., no significant correlation between maximum fall in FEV₁ and PC₂₀ methacholine was found.

FENO Determinations

Mean FENO values at baseline were 35.78 ± 37.60 ppm; 24 hr after bleach SIC, these values were 39 ± 34 ppm ($P = 0.043$).

In three patients with positive SIC, FENO values measured at baseline and 24 hr after the SIC increased from 46 to 67 ppm, from 100 to 115 ppm and from 8 to 13 ppm, respectively.

Differential Sputum Counts

Thirty-eight sputum samples from patients were analyzed. Sputum samples had less than 10% squamous epithelial cells and cell viability was greater than 85%. No statistical differences were obtained, except when comparing eosinophil counts. A significant decrease was observed after SIC in patients with or without positive methacholine tests in comparison with baseline counts ($8.22 \pm 7.7\%$ vs. $17.53 \pm 13.12\%$, $P = 0.035$, respectively). This difference is likely due to the increase of neutrophils after SIC. Concerning activated basophils or lymphocytes, no statistical differences were found when comparisons were carried out. Due to a low number of smokers, we did not analyze these patients separately.

Short-Term Personal Exposure Measurements of Airborne Chlorine

Chlorine airborne concentrations during the bathroom-cleaning simulation are shown in Figure 2. For a 5-min cleaning, peak concentrations of 1.41 and 1.22 ppm of chlorine were obtained. For a period of about 20 min, chlorine concentration was above 0.5 ppm.

DISCUSSION

Introduction

Symptoms of obstructive lung disease in domestic cleaning staff have been related to the use of bleach and other irritant cleaning products [Zock et al., 2001; Medina-Ramon et al., 2005, 2006; Zock, 2005]. However, very few studies have demonstrated the effect of bleach on the airway by means of SIC [Rotman et al., 1983; D'Alessandro et al., 1996]. D'Alessandro et al. found that a chlorine inhalation of 1.0 ppm induced an acute, short-term fall in airflow and an increase in airway resistance in both normal subjects and subjects with BHR. However, the authors observed a significantly greater response among the group of subjects with BHR as compared with normal subjects. Nevertheless, they did not find any meaningful response among subjects with or without BHR when the subjects were exposed to 0.4 ppm of chlorine. In Rotman's study [1983], in which eight healthy volunteers were exposed to 1.0 ppm of chlorine gas, one non-asthmatic subject did experience shortness of breath and wheezing. In this subject, FEV₁ levels fell from 4.4 to 1.9 L, while airway resistance increased by 300%. The researchers also found that there was an overall group decrease in airflow as well as an increase in airway resistance. Of note, when the subject who exhibited the exaggerated response to 1.0 ppm of chlorine was exposed to 0.5 ppm of chlorine, his sRaw doubled after 4 hr, although there was no significant group-wide change.

TABLE II. Results of Functional and Inflammatory Parameters Before and After Inhalation Challenges

Patients #	FENO, ppm		PC ₂₀ methacholine at baseline	PC ₂₀ methacholine after SIC	SIC placebo	Maximum fail FEV ₁ (% baseline) during placebo	SIC with bleach	Maximum fail (% baseline) during SIC	% Sputum neutrophil at baseline	% Sputum neutrophils after SIC	% Sputum eosinophils at baseline	% Sputum eosinophils after SIC	% Sputum macrophages at baseline	% Sputum macrophages after SIC
	baseline	SIC												
1	123	v95	1.35	0.281	neg	8	neg	17	25	26	5	4	67	67
2	8	21	5.8	0.083	neg	4	neg	13	49	21	20	27	29	50
3	46	67	0.125	0.83	neg	4	DAR	40	37	70	19	6	41	21
4	11	15	8	8.6	neg	5	neg	15	61	59	5	2	30	36
5	25	22	5.68	3.34	neg	3	neg	12	62	92.	5	3	28	2
6	5	7	2.7	1.875	neg	8	neg	17	61	35	5	2	24	12
7	8	12	0.37	0.37	neg	5	neg	9	74	76	3	4	15	16
8	110	115	>16	>16	neg	3	LAR	33	51	31	10	18	34	47
9	11	12	>16	>16	neg	2	neg	12	29	34	8	20	60	43
10	8	13	>16	>16	neg	4	LAR	34	36	17	11	45	50	31
11	11	27	>16	>16	neg	3	neg	12	59	42	7	14	30	38
12	108	111	>16	>16	neg	1	neg	4	45	62	11	4	34	21
13	51	52	>16	>16	neg	1	neg	2	45	54	6	5	8	30
14	26	20	2	1	neg	2	neg	4	48	62	16	7	33	28
15	35	59	0.83	0.156	neg	1	neg	3	23	34	15	14	57	48
16	13	22	6	4	neg	1	neg	3	49	65	20	8	28	24
17	49	46	>16	>16	neg	0	neg	0	40	43	4	13	50	40
18	16	16	>16	>16	neg	1	neg	5	32	33	23	29	42	35
19	16	24	>16	10	neg	1	neg	4	27	31	7	6	60	58

Neg, negative; DAR, dual asthmatic reaction; LAR, late asthmatic reaction.
Patients 1 – 13 are cleaning personnel.

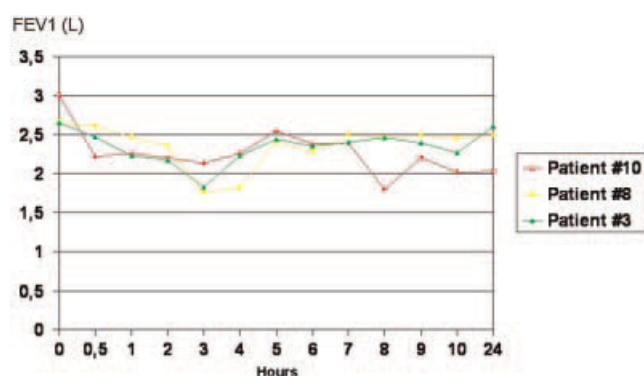


FIGURE 1. FEV₁ follow-up of patients with a positive response to bronchial challenge with chlorine.

In our study, we observed three janitorial workers with a positive SIC after inhaling 0.4 ppm of chlorine. Two of the subjects had negative methacholine tests both before and after the SIC. In the cases with positive SIC to bleach inhalation, we observed an increase in neutrophils 24 hr after the challenge in one patient with the dual asthmatic reaction, while the two others (with late asthmatic response) experienced an increase of eosinophils. None of them experienced a significant increase in methacholine PC₂₀ or FENO values. The mean maximum fall in FEV₁ during the 24-hr monitoring period for challenge testing with bleach showed a significantly greater decrease than that which was observed during the placebo challenge. We did not find that the group with BHR underwent a significantly greater decrease in FEV₁ than subjects without BHR. Of all the patients challenged with bleach, only one subject had a ≥ 2 -fold increase in methacholine PC₂₀ 24 hr after SIC. When analyzing this alongside previous findings, it appears that chlorine inhalation below the recommended 8-hr occupational exposure level has the capacity to induce an exaggerated bronchial obstruction in some patients whether they have BHR or not, though no significant BHR increase is

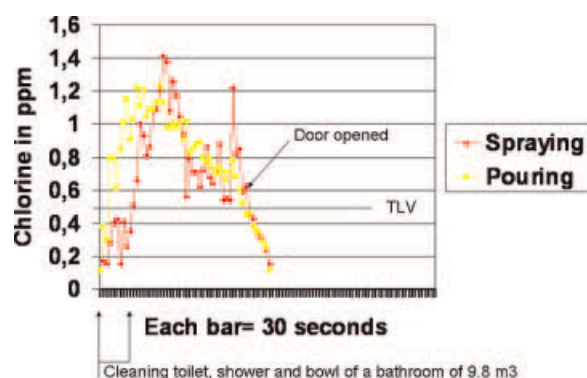


FIGURE 2. Chlorine concentrations during cleaning of a bathroom measuring 9.8 m³ attained by spraying or pouring commercial bleach (5% chlorine). Cleaning lasted 5 min.

seen in the majority of the subjects. As mentioned previously, the study conducted by D'Alessandro et al. found no meaningful response among subjects with or without BHR when exposed to 0.4 ppm of chlorine. This may be due to differences in the susceptibility of the individuals included in these studies or simply due to chance.

As for inflammatory markers, we found a significant increase in FENO values 24 hr after SIC with bleach in comparison with baseline levels, though this difference is not considered to be clinically relevant. This increase is consistent with the notion that eosinophils have no influence on the respiratory effects of chlorine inhalation. A sputum cell count analysis showed no meaningful impact brought about by the chlorine challenge. We can only demonstrate an insignificant tendency toward a higher percentage of neutrophils after SIC in patients with BHR.

We measured airborne chlorine concentrations during the cleaning of a bathroom of 9.8 m³. The maximum airborne chlorine concentration during the 5-min task was 1.42 ppm, which was higher than the figure reported by Medina-Ramon et al. [2006] For about 20 min, the chlorine concentration was above the threshold limit value (TLV) of 0.5 ppm. This experiment demonstrates that, while cleaning a household with commercial bleach, a subject may be exposed to potentially irritant concentrations of chlorine either by using a spray device or by pouring the bleach over the surfaces to be cleaned.

The laboratory conditions that we studied created lower chlorine-exposure levels than the ones we obtained while simulating household cleaning, and therefore may not be directly relevant to many occupational or environmental exposure scenarios. This lack of representativeness is increased in situations of much higher and much briefer exposure. Therefore, our findings should be interpreted in the context of a controlled bronchial challenge, though their clinical relevance and generalizability to non-laboratory exposures should not be overlooked. The effects of inhaling other irritants while cleaning may also contribute to a worsening of pulmonary function response in cleaning employees. Another limitation of this study is the number of patients included. However, our findings may explain the appearance of asthma-like respiratory symptoms in cleaning workers exposed to bleach during janitorial tasks at home or in the workplace, thereby furthering the claim that respiratory symptoms are related to some degree of airway obstruction. This effect is independent of a patient's previous degree of BHR and is likely due to an irritant effect. No significant changes in FVC were observed after bleach challenge ruling out a restrictive reaction.

In conclusion, our data suggest that subjects with or without BHR manifest an exaggerated, non-specific FEV₁ decrease following bleach (chlorine gas) inhalation at a chlorine-concentration level of 0.4 ppm, which is below the 8-hr permissible occupational exposure level. Some subjects

experience an exaggerated reaction (positive SIC) to bleach inhalation. This should not be extrapolated to higher exposure concentrations or longer duration at lower exposure levels. Further delineation of the respiratory dose–response to chlorine will be important in order to adequately protect high-risk populations from exposure to this common occupational and environmental irritant.

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