Impact of Low Dose Chlorine Inhalation in Healthy Humans: A Pilot Study

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Palabras clave: Cloro. Inflamación de vía aérea. Asma inducida por irritantes.

Low-dose exposure to chlorine occurs frequently during activities such as routine attendance at swimming pools or usage of domestic and/or industrial cleaners. Although some human studies have looked at the effects of low-dose chlorine exposure on airway function, few studies have reported the impact of low-dose chlorine exposure on airway inflammation in humans [3,4]. A better understanding of these mechanisms is critical for improving the prevention and treatment of injuries induced by chlorine inhalation.

The objective of the present study was to investigate the effect of low-dose chlorine exposure on lung function and airway inflammation in healthy individuals.

We performed a pilot experimental crossover study comparing the effect of low-dose chlorine exposure and fresh air exposure on respiratory function and airway inflammation. Participants were exposed to gaseous chlorine and fresh air with a 2-week washout period at Hôpital du Sacré-Coeur de Montréal, Montreal, Canada between February and June 2017.

Eligible participants were 18 years or older and healthy. All participants provided informed consent. The study was approved by the Research Ethics Committee of Sacré-Coeur Hospital.

Spirometry [5], methacholine inhalation challenge test [6], and sputum induction were performed at the first visit. Sputum was induced and processed for total and differential cell counts as previously described [7]. Supernatant was stored for subsequent measurements of oxidative stress markers, cysteinyl leukotrienes, anti-inflammatory prostaglandins, and potential mediators of remodeling. Forty-eight hours later, the participants were exposed either to fresh air or to 1 ppm of gaseous chlorine for 15 minutes, the threshold value accepted as safe in Canada [8], using a previously described closed-circuit apparatus [9]. Spirometry was repeated immediately after the end of the exposure period. Thirty minutes following the exposure, participants underwent sputum induction. Twenty-four hours after the exposure, participants once again underwent spirometry, methacholine challenge test,

Table. Inflammatory Parameters Before and After Fresh Air and Chlorine Exposure

<table>
<thead>
<tr>
<th></th>
<th>24 h Pre-exposure</th>
<th>24 h Post-exposure</th>
<th>30' Postexposure</th>
<th>24 h Pre-exposure</th>
<th>24 h Post-exposure</th>
<th>30' Postexposure</th>
<th>24 h Pre-exposure</th>
<th>24 h Post-exposure</th>
<th>30' Postexposure</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC_{20}, mg/mL</td>
<td>96 (87.0)</td>
<td>--</td>
<td>93.5 (96.0)</td>
<td>.79</td>
<td>96.0 (72.0)</td>
<td>--</td>
<td>94.0 (78.0)</td>
<td>.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FeNO, ppb</td>
<td>17.25 (6.0)</td>
<td>--</td>
<td>16.0 (5.3)</td>
<td>.93</td>
<td>15.5 (5.0)</td>
<td>--</td>
<td>15.3 (7.0)</td>
<td>.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCC, 106 c/mL</td>
<td>1.6 (1.3)</td>
<td>2.9 (3.8)</td>
<td>1.4 (0.8)</td>
<td>.11</td>
<td>11.1 (0.5)</td>
<td>3.68 (3.2)</td>
<td>1.4 (0.7)</td>
<td>.01</td>
<td></td>
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</tr>
<tr>
<td>Eosinophils, %</td>
<td>0.0 (0.3)</td>
<td>0.0 (0.3)</td>
<td>0.1 (0.3)</td>
<td>.73</td>
<td>0.1 (0.3)</td>
<td>0 (0.25)</td>
<td>0 (0.25)</td>
<td>.81</td>
<td></td>
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<tr>
<td>Neutrophils, %</td>
<td>35.9 (49.3)</td>
<td>66.9 (30.3)</td>
<td>29.4 (30.8)</td>
<td>.16</td>
<td>36.8 (46.8)</td>
<td>64.6 (36.0)</td>
<td>45.9 (50.5)</td>
<td>.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrophages, %</td>
<td>63.3 (47.3)</td>
<td>30.8 (30.0)</td>
<td>67.5 (31.8)</td>
<td>.19</td>
<td>43.0 (13.8)</td>
<td>33.9 (42.3)</td>
<td>53.5 (51.8)</td>
<td>.88</td>
<td></td>
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<tr>
<td>Lymphocytes, %</td>
<td>0.5 (1.3)</td>
<td>0.3 (0.5)</td>
<td>0.4 (1.0)</td>
<td>.86</td>
<td>0.9 (0.8)</td>
<td>0.3 (0.8)</td>
<td>0 (0.75)</td>
<td>.08</td>
<td></td>
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<tr>
<td>Bronchial cells, %</td>
<td>0.5 (0.5)</td>
<td>0.3 (1.3)</td>
<td>0.5 (2.0)</td>
<td>.80</td>
<td>0.8 (0.8)</td>
<td>0.3 (0.8)</td>
<td>0.5 (1.0)</td>
<td>.26</td>
<td></td>
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<tr>
<td>Epithelial cells, %</td>
<td>5.6 (8.4)</td>
<td>7.9 (7.9)</td>
<td>6.8 (7.0)</td>
<td>.93</td>
<td>5.0 (4.2)</td>
<td>5.1 (0.5)</td>
<td>12.8 (11.4)</td>
<td>.29</td>
<td></td>
<td></td>
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</table>

Abbreviations: FeNO, fractional exhaled nitric oxide; PC_{20}, provocative concentration of methacholine inducing a 20% fall in FEV_{1}; TCC, total cell count.

aData are presented as median (IQR).
and sputum induction. After a washout period of 2 weeks, the procedures were repeated, but the participants were exposed to the alternate exposure condition. The order of exposures (chlorine first followed by clean air vs clean air first followed by chlorine) was randomized and balanced.

Forced expiratory volume in the first second (FEV₁), sputum total and differential cell counts, and selected soluble biomarkers were compared between baseline, immediate postexposure, and 24 hours postexposure, whereas PC₂₀ and FeNO were compared at baseline and 24 hours postexposure.

All statistical analyses including demographic and clinical variables, FEV₁, FeNO, PC₂₀, total sputum, differential cell counts, and biomarkers were performed using the Kruskal-Wallis test for continuous variables and the χ² for categorical variables, as appropriate. Exposure condition and time-points were taken into account using a crossover design. Statistical analyses were completed using STATA software.

Six healthy individuals were studied (5 women [83.3%]). Median (IQR) age was 27.5 (8.0) years. Five participants (83.3%) had never smoked, and 1 was an ex-smoker with a median (IQR) of 0 (0.5) pack years. Five participants (83.3%) were atopic.

The median (IQR) of the FEV₁ (% predicted), FEV₁ (L), and the FEV₁/FVC (%) values were 114.0 (17.6) %, 3.2 (0.7) L, and 83.7 (5.4) %, respectively.

No differences were found before or after exposure to fresh air and before exposure to chlorine in terms of lung function and airway responsiveness. The total cell count increased slightly immediately after chlorine exposure. The same trend was observed after fresh air exposure, although the difference was not statistically significant. IL-8 tended to increase slightly after both fresh air exposure and chlorine exposure. Neutrophils tended to increase after exposure to both fresh air and chlorine, although, once again, the difference was not statistically significant (Table).

D’Alessandro et al [3] reported significant reductions in FEV₁ (–350 mL) and increases in specific airway resistance in 5 healthy individuals and 5 patients with airway hyperresponsiveness after chlorine exposure at 1 ppm for an hour. Sastre et al [4] investigated 13 cleaners complaining of work-related asthma symptoms when exposed to cleaning agents, 3 asthmatic controls, and 3 healthy individuals. The authors assessed sputum differential cell counts and FeNO levels in addition to pulmonary function after a 60-minute hour. Sastre et al [4] investigated 13 cleaners complaining of work-related asthma symptoms when exposed to cleaning agents, 3 asthmatic controls, and 3 healthy individuals. Higher doses of chlorine should be tested to study the impact of chlorine gas on airway inflammation.

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In conclusion, exposure to 1 ppm of chlorine for 15 minutes did not induce significant changes in airway function or inflammation compared with fresh air exposure in healthy individuals. Higher doses of chlorine should be tested to study the impact of chlorine gas on airway inflammation.

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**Conflicts of Interest**

CL has received consultancy fees from the following companies: GlaxoSmithKline, AstraZeneca, TEVA innovation, Metafarm, and Sanofi Genzyme. She has also received research grants from AstraZeneca and TEVA innovation. IO has received consultancy fees from GlaxoSmithKline and fees for talks from Novartis, AstraZeneca, Boehringer, and TEVA innovation. He has also received research grants from Mundipharma.

**References**

Selection of Biologics in Severe Asthma: A Multifaceted Algorithm

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As occurs in other diseases, asthma can now be treated with biologics. The first agent used was omalizumab (in 2004), which was followed by mepolizumab, reslizumab, and benralizumab, with dupilumab recently added to the list [1]. These biologics have different mechanisms of action: omalizumab targets immunoglobulin E (IgE); mepolizumab and reslizumab block interleukin 5 (IL-5); benralizumab binds the α chain of the IL5 receptor (IL5RA) and induces natural killer cells to drive apoptosis of cells bearing the receptor; and dupilumab targets IL-4RA, which is shared by IL-4 and IL-13, thus blocking the signaling of both cytokines.

Various algorithms for selection of biologics in severe asthma have been published [2-5]. However, since there are no head-to-head comparison studies, we propose an algorithm for the selection of biologics in adult patients with severe asthma based on clinical evidence, post hoc analysis, and available biomarkers (Figure).

1. Before treatment with biologics, the diagnosis of asthma should be reconsidered, proper adherence and inhalation technique should be ensured, allergen and trigger avoidance should be tried, and appropriate treatment of comorbidities should be provided.

2. The patient should be diagnosed with uncontrolled severe asthma. Severe asthma is defined as “asthma that requires treatment with high-dose inhaled corticosteroids and with a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy” [2]. This corresponds to GEMA (Spanish Guidelines on the Management of Asthma) treatment steps 5 and 6 [6]. The diagnosis of uncontrolled asthma should fulfill 1 of the following requirements: (1) Asthma Control Test <20 or Asthma Control Questionnaire >1.5; (2) ≥2 asthma attacks that had required ≥2 bursts of systemic corticosteroids; (3) at least 1 hospitalization, 1

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