The airways effects of inhaled chlorbutol in asthmatic subjects

H. Windom, C. Burgess, J. Crane, R. Beasley

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ABSTRACT: Chlorbutol is an antibacterial and antifungal agent incorporated in terbutaline (Bricanyl) nebulizer solution. Ten stable asthmatic subjects underwent bronchial challenge testing, according to a double-blind protocol. Patients inhaled doubling concentrations of either methacholine (0.13-4.0 mg·ml⁻¹) or chlorbutol (0.16-5.0 mg·ml⁻¹) for 2 min until the forced expiratory volume in one second (FEV₁) had fallen by 20% from baseline. If this had not occurred following the administration of the final concentration, then this highest concentration was repeated for 4 min. The nine subjects completing the study had a geometric mean provocation concentration producing a 20% fall from baseline (PC₂₀) of methacholine of 0.16 mg·ml⁻¹ (range <0.125-0.475 mg·ml⁻¹). After inhalation of 2.5 mg·ml⁻¹ chlorbutol one subject experienced a fall in FEV₁ >20%. In the remaining eight subjects, inhalation of chlorbutol did not affect airway calibre. We conclude that chlorbutol, in the concentration present in Bricanyl nebulizer solution, has no clinically significant effect on airway calibre.


The administration of β-adrenergic agonists by nebulization forms the mainstay of the hospital management of asthma. In addition, it has become increasingly popular in the domiciliary setting, with the proliferation of less expensive portable machines [1]. Historically, manufacturers of nebulizer solutions have faced problems with paradoxical bronchoconstriction secondary to the formulation of the solutions, relating to the osmolarity and acidity [2, 3]. Complications from bacterial contamination of both the solutions and the nebulizer equipment have also frequently been reported [3, 4].

Inhalation of Atrovent nebulizer solution containing the preservatives benzalkonium chloride and edetic acid caused bronchoconstriction in some asthmatic subjects [5], and their removal enhanced the speed of onset and the magnitude of bronchodilation of the Atrovent solution [6]. These findings led to the development and marketing of "preservative-free" Atrovent, and more recently "preservative-free" β-agonist nebulizer solutions such as salbutamol and the fenoterol-ipratropium bromide combination (Duvent).

Chlorbutol, is an antibacterial and antifungal agent which is incorporated in terbutaline (Bricanyl) nebulizer solution [7, 8]. Chlorbutol is present in a concentration of 5 mg·ml⁻¹ in the stock (terbutaline 10 mg·ml⁻¹) solution, for which it is recommended that 0.5 ml be diluted to a total volume of 5.0 ml with sterile physiological saline. Thus, chlorbutol is present in a concentration of 0.5 mg·ml⁻¹ when terbutaline nebulizer solution is administered according to the manufacturer’s recommendations.

In this study we have undertaken bronchial provocation testing with chlorbutol in asthmatic subjects to determine its airways effects. Concomitant challenge testing with methacholine was performed to enable a double-blind study design to be employed, and also to quantify nonspecific bronchial responsiveness.

Methods

Ten stable asthmatic subjects were enrolled in the study (table 1). None of the subjects possessed a home nebulizer, nor had any been previously exposed to nebulized terbutaline. Patients were recruited from a group of volunteers, none of whom reported having a previous idiosyncratic reaction to nebulized β-agonists. The study was approved by the Research Ethical Committee of the Wellington Hospital Board and written informed consent was obtained from each subject.

Each subject attended the laboratory on two occasions after withholding their β-agonist medication for a minimum of 6 h. They were randomly assigned double-blind to bronchial provocation challenge testing with methacholine or chlorbutol. Chlorbutol was provided as the hydrochloride salt (MW 212.92 g·mol⁻¹) in a 5 mg·ml⁻¹ solution (0.0235 M). On two separate
occasions, the patients inhaled doubling concentrations of either methacholine (0.125-4.0 mg·ml⁻¹) or chlorbutol (0.157-5.0 mg·ml⁻¹) through a face mask during tidal breathing for 2 min. Increasing concentrations of each solution were inhaled until the forced expiratory volume in one second (FEV₁) had fallen by >20%, and if this had not occurred following the administration of the final concentration, this concentration was repeated for 4 min to achieve an equivalent of 8 mg·ml⁻¹ of methacholine or 10 mg·ml⁻¹ chlorbutol. All solutions had a starting concentration of 0.125 mg·ml⁻¹, this concentration was repeated for 4 min by asthmatic subjects [5].

The airway response was expressed as a percentage change in FEV₁ from baseline value. The provocation concentration of inhaled solution which produced a 20% fall in FEV₁ (PC₁₀) was derived by linear interpolation from the log concentration-FEV₁ response curve.

Skin-prick testing was performed to four common allergens and chlorbutol (2.5 and 5.0 mg·ml⁻¹). A skin test was considered to be positive if a weal >3 mm occurred after 20 min. Atopy was considered to be present if a subject had a positive skin test to one or more allergens.

Results

Nine subjects completed the study (subject 4 withdrew due to worsening asthma requiring a course of prednisone). There was no significant difference between the baseline FEV₁ measured on the different study days.

All subjects had markedly increased bronchial reactivity in response to methacholine, with a geometric mean PC₁₀ of 0.16 mg·ml⁻¹ (range <0.125-0.475 mg·ml⁻¹). For all subjects, the mean (range) change in FEV₁ after inhalation of chlorbutol in a concentration of 0.64 mg·ml⁻¹ was +2.5% (-10.4 to +10.4%). One subject (No. 9), experienced a fall in FEV₁ of >20% after 2 min inhalation of 2.5 mg·ml⁻¹ chlorbutol. On repeat challenge testing with chlorbutol, this subject experienced a fall in FEV₁ of >20% after 2 min inhalation of 5.0 mg·ml⁻¹ chlorbutol. In the remaining eight subjects, inhalation of increasing concentrations of chlorbutol did not affect airway calibre, resulting in a mean (range) change in FEV₁ of +3% (-13 to +19%) after 4 min of the 5 mg·ml⁻¹ solution.

All nine subjects were atopic. No subjects had a positive skin prick test with chlorbutol up to a concentration of 5 mg·ml⁻¹.

Discussion

In this study we have demonstrated that repeated inhalation of the preservative chlorbutol is well tolerated by asthmatic subjects. In all but one subject studied, there was no significant adverse airways response following inhalation of chlorbutol in a concentration ten times greater than that present when terbutaline (Bricanyl) nebulizer solution is administered according to the manufacturer's recommendations. This contrasts with the airways response to both benzalkonium chloride and edetic acid, which cause dose-dependent bronchoconstriction in asthmatic subjects [5].

One subject did, however, experience a significant fall in FEV₁ after inhalation of chlorbutol in a concentration of 2.5 mg·ml⁻¹. In this subject, the concentration of chlorbutol required to cause a 20% fall in FEV₁ was about ten times greater than the PC₁₀ for methacholine. A rechallenge with chlorbutol in this subject again resulted in a 20% fall in FEV₁ within the range of concentration tested. This subject's lack of previous exposure to chlorbutol and inability to mount a reaction to skin testing with chlorbutol, would support the view that the adverse airways response was not due to immediate immunoglobulin E (IgE)-dependent hypersensitivity. It

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Atopy</th>
<th>PC₁₀ meth.</th>
<th>PC₁₀ chlor.</th>
<th>Therapy</th>
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<tr>
<td>1</td>
<td>26</td>
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<td>0.152</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>M</td>
<td>+</td>
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<td>0.288</td>
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<tr>
<td>3</td>
<td>21</td>
<td>M</td>
<td>+</td>
<td>95</td>
<td>0.136</td>
<td>S,B</td>
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<tr>
<td>4</td>
<td>34</td>
<td>M</td>
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<td>81</td>
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<tr>
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<td>24</td>
<td>F</td>
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<td>109</td>
<td>0.148</td>
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<tr>
<td>6</td>
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<td>M</td>
<td>+</td>
<td>68</td>
<td>&lt;0.125</td>
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<td>M</td>
<td>+</td>
<td>83</td>
<td>0.475</td>
<td>S,B</td>
</tr>
</tbody>
</table>

WD: withdrew from study; F: female; M: male; S: salbutamol; B: beclomethasone; D: fenoterol/ipratropium bromide; FEV₁: forced expiratory volume in one second; PC₁₀: provocative concentration producing a 20% fall in FEV₁; meth: methacholine; chlor: chlorbutol.
remains to be determined, however, whether this degree of airways effect due to chlorbutol would affect the overall airways response when inhaled in combination with a potent β₂-adrenergic agonist such as terbutaline.

We conclude that chlorbutol has no effect on airway calibre, when inhaled by asthmatic subjects in the same concentration as that present when Bricanyl nebulizer solution is administered according to the manufacturer’s recommendations.

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References