Effect of tonicity of nebulised colistin on chest tightness and pulmonary function in adults with cystic fibrosis

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Abstract

Background – Inhalation of hypertonic nebulised colistin causes chest tightness and is a reason for discontinuing the treatment. This study examines the relationship of chest tightness and change in lung function in response to the inhalation of a range of tonicities of nebulised colistin and their influence on patients’ preference.

Methods – Twenty seven adult patients with cystic fibrosis and a mean forced expiratory volume in one second (FEV,) of 54% predicted (range 24–98) were studied. They inhaled a nebulised solution of hypertonic, isotonic, and hypotonic colistin over three consecutive days in random order in a double blind fashion. Measurements of chest tightness, using a visual analogue scale (VAS), and FEV, were recorded before and 0, 15, 30, 60, and 90 minutes following inhalation. The solution preferred by each patient was determined at the end of the three days.

Results – All tonicities caused a significant fall in FEV, % predicted and an increase in chest tightness, with no differences between the solutions. However, the mean (SE) time to the maximum fall in FEV, % predicted was significantly different between the solutions (hypertonic 7.8 (2.1) min, isotonic 19.2 (5.5) min, and hypotonic 34.2 (5.9) min) with a mean difference (95% CI) between hypotonic and hypertonic solutions of 28.04 (14.6 to 41.5) min, between isotonic and hypertonic solutions of 12.0 (–0.1 to 24.1) min, and between hypotonic and isotonic solutions of 15.6 (1.8 to 29.4) min. Positive correlations existed for the maximum fall in FEV, % predicted between the hypertonic and isotonic solutions (r = 0.62, p <0.001) and between the hypotonic and isotonic solutions (r = 0.64, p <0.001). There was no correlation between the objective and subjective measurements for any solution. The patients’ preference varied.

Conclusions – All tonicities of colistin caused equal symptoms of chest tightness and reduction in pulmonary function. It is recommended that the patient is challenged with nebulised colistin before prescription of the drug and that the challenge is preceded by an inhaled bronchodilator. Most of the patients preferred the isotonic or hypotonic solutions. The isotonic solution reflects a fall in FEV, representative of all the solutions. The fall in FEV, to the hypotonic solution occurred over a longer period and may be better tolerated by some patients.

Keywords: tonicity, nebulised colistin, cystic fibrosis.

The benefits of nebulised antibiotics in cystic fibrosis include a reduction in the rate of decline of lung function and in the number of hospital admissions for patients with severe disease, a reduction in positive sputum cultures in patients recently colonised with Pseudomonas aeruginosa, and eradication of the organism. Colistin sulphomethate, a polymyxin antibiotic, may be the drug of choice because resistance is uncommon and it is the only antibiotic licensed for inhalation in the UK. Hypertonic nebulised antibiotics including colistin can induce bronchoconstriction in patients with cystic fibrosis even when the treatment is preceded by inhalation of a bronchodilator. Bronchoconstriction may be a reason for poor compliance and discontinuing the therapy. Previous work has shown that immediately perceived benefits or adverse symptoms influence compliance with treatment. A subject’s perception of chest tightness may differ from objective measurements and therefore might influence compliance irrespective of objective changes in lung function.

Colistin is a dry powder formulation requiring reconstitution with sterile water or 0.9% sodium chloride before aerosol inhalation. The choice of solvent will influence compliance irrespective of objective changes in lung function.

The aims of this study were to examine the relationship between the objective measurement of lung function and the subjective measurement of chest tightness and their influence on patients’ preference in response to hypertonic, isotonic, and hypertonic solutions of nebulised colistin. We hypothesised that isotonic nebulised colistin would not induce bronchoconstriction and would be the treatment preferred by the patients.

Methods

Patients

Thirty adult patients (23 men) with cystic fibrosis participated in the study when they were...
Table 1 Differences in mean values (95% CI) for maximum fall in FEV₁ (% predicted) and maximum change in VAS (%) between the solutions

<table>
<thead>
<tr>
<th>Tonicity of nebulised colistin in cystic fibrosis</th>
<th>Maximum fall in FEV₁ (% predicted)</th>
<th>Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertonic vs isotonic</td>
<td>7.2 ± 6.4</td>
<td>0.77</td>
<td>−0.85 to 2.4</td>
</tr>
<tr>
<td>Hypertonic vs hypotonic</td>
<td>7.2 ± 5.5</td>
<td>1.60</td>
<td>−0.41 to 3.6</td>
</tr>
<tr>
<td>Isotonic vs hypotonic</td>
<td>6.4 ± 5.5</td>
<td>0.85</td>
<td>−0.37 to 2.0</td>
</tr>
</tbody>
</table>

Maximum change in VAS (%)

<table>
<thead>
<tr>
<th>Tonicity of nebulised colistin in cystic fibrosis</th>
<th>Maximum change in VAS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertonic vs isotonic</td>
<td>6.6 ± 10.8</td>
</tr>
<tr>
<td>Hypertonic vs hypotonic</td>
<td>6.6 ± 8.6</td>
</tr>
<tr>
<td>Isotonic vs hypotonic</td>
<td>10.8 ± 8.6</td>
</tr>
</tbody>
</table>

Results

Twenty seven patients (20 men) completed the study; two were withdrawn because their baseline measurements failed to fall within 15% of day 1, and one further patient withdrew. The mean age was 23 years (range 17–35). The mean FEV₁ was 54% predicted (range 24–98) with mean absolute values of 2.1 litres (range 0.8–3.95). Of the 27 patients, 18 used oral bronchodilators, 23 inhaled bronchodilators, and 12 inhaled steroids.

Tonicity of colistin

Solutions of colistin which were easily reconstituted for home use (two million units (MU) dissolved in 4 ml solvent) were analysed for toxicity by the Department of Biochemistry. The osmolality of 2 MU colistin in 4 ml 0.9% sodium chloride was 417 mmol/kg (hypertonic), of 2 MU colistin in 2 ml 0.9% sodium chloride plus 2 ml sterile water was 264 mmol/kg (isotonic), and of 2 MU colistin in 4 ml sterile water was 150 mmol/kg (hypotonic).

Judged to be clinically stable. Details of bronchodilator and inhaled steroid use were recorded. Patients were recruited on their willingness to take part and were chronically colonised with *Pseudomonas aeruginosa*.

Study design

On each study day oral and inhaled bronchodilators were withheld for 12 hours. Chest clearance was performed prior to the baseline measurements of a visual analogue scale (VAS) score of chest tightness and forced expiratory volume in one second (FEV₁) using a dry bellows spirometer (Vitalograph Ltd, UK). The patients then inhaled 4 ml of either a hypertonic, isotonic, or hypotonic solution of colistin on three consecutive days at the same time of day. The study was randomised and double blind. All solutions were delivered using a SideStream nebuliser with a mouthpiece and CR60 compressor (Medic-Aid, Pagham, Sussex, UK). The VAS score and FEV₁ were repeated immediately and 15, 30, 60, and 90 minutes after nebulisation. At the end of the three-day study period the patients were asked to indicate which solution they preferred to inhale (day 1, day 2, day 3 or no preference).

Maximum changes

The mean baseline values of VAS scores and FEV₁ were not significantly different for the three solutions. There were significant mean (SE) baseline to maximum falls in percentage predicted FEV₁ of 7.2 (1.0), 6.4 (0.6), and 5.5 (0.7) and maximum increases in VAS scores of 6.6 (3.0), 10.8 (3.0), and 8.6 (2.3) for the hypertonic, isotonic, and hypotonic solutions, respectively. However, there were no differences in the magnitude of these changes between the solutions (table 1). The maximum fall in FEV₁, occurred at different time points for each solution: 7.8 (2.1), 19.2 (5.5), and 34.2 (5.9) min for the hypertonic, isotonic, and hypotonic solutions, respectively (fig 1). The time to the fall was significantly different between the solutions with a mean difference (95% CI) between the hypertonic and hypotonic solutions of 28.04 (14.6 to 41.5) min, between the isotonic and hypertonic solutions of 12.0 (0.1 to 24.1) min, and between the hypertonic and hypotonic solutions of 15.6 (1.8 to 29.4) min. There were no differences in the VAS scores between the solutions.

Relationship between maximum fall in FEV₁ (% predicted) and VAS and baseline FEV₁ (% predicted)

For the maximum fall in FEV₁ there were positive correlations between hypertonic and isotonic solutions ($r = 0.62, p < 0.001$) and between isotonic and hypotonic solutions ($r =$ 0.37, $p =$ 0.007).

![Figure 1](http://thorax.bmj.com)
function was not associated with perception earlier after inhalation. For some patients an between the maximum fall in FEV₁ and base-

imum fall in FEV₁ and the increase in the VAS was compared with the other solutions in the falls by the hypertonic and hypotonic solutions. a tendency for patients not to prefer the hyper-

and may have accounted for the di-
erence.1 Hodson ME, Penketh ARL, Batten JC. Aerosol carbenicillin cause chest tightness and bronchoconstriction. The results of this study show that all three but the patients’ preference ... induce bronchoconstriction was not there-

fore supported. Chua et al showed a greater fall in FEV₁, with increasing toxicity of saline.10 In agree-

cement with our study, their patients also showed a fall with the hypertonic solution. Non-isotonic solutions are known to cause release of hist-

amine by changing the osmotic load around mast cells.10 In contrast to our findings, Schoef-

fel et al found no reduction in FEV₁ with isotonic saline. Colistin causes mast cell de-
genration in vitro which may account for the bronchoconstriction induced by the isotonic solution in our study.12 The pH of the solutions did not vary and colistin is preservative free, therefore excluding these factors as possible mechanisms of bronchoconstriction. In this study all bronchodilators were with-
held and all patients showed a fall in FEV₁ with all the solutions. The long term effect of repeated bronchoconstriction is not known. If nebulised colistin is recommended to ensure improved disease control, it is important to protect against bronchoconstriction. Sal-

butamol has been shown to be more effective than sodium cromoglycate, possibly through its bronchodilator activity in addition to in-
hibition of mast cell degranulation.13

All patients perceived an increase in chest tightness for all solutions but, as in previous studies, there was no correlation between the maximum change in FEV₁ and VAS scores.8,9 The reasons for patients preferring a particular toxicity are difficult to determine. There was a tendency for patients not to prefer the hypertonic solution. When the hypertonic solution was compared with the other solutions in the group as a whole the fall in FEV₁ occurred earlier after inhalation. For some patients an immediate fall in FEV₁ may be less tolerable than an equivalent fall which occurs gradually over a longer time period such as occurred with the hypertonic solution. In our previous study maximum bronchoconstriction occurred im-
mEDIATELY after inhalation in most patients and may therefore be a reason for the intolerance of the hypertonic solution.3

Patients with cystic fibrosis require a demanding programme of self care and adherence to any treatment is likely to be influenced by benefits and adverse symptoms. It is therefore important to measure and minimise any ad-

verse effects of aerosol therapy before pre-
scription of the drug.

We have shown that all toxicities of colistin cause chest tightness and bronchoconstriction. but the patients’ preference varied. In the clinical setting it is impractical to challenge every patient to each toxicity. Since all toxicities cause chest tightness, prior spirometric testing before and after inhalation at intervals up to 30 minutes is recommended before prescription. The isotonic solution used as a challenge will indicate a fall in FEV₁, representative of the other solutions. The fall in FEV₁ for the hypo-

tonic solution occurred over a longer time period and may be considered an alternative choice if the isotonic solution is not tolerated.

2 Littlewood JM, Miller MG, Ghonheim AT, Ramsden CH. Nebulised colomycin for early pseudomonas colonisation in cystic fibrosis. Lancet 1985;i:865.