Is Salamol less effective than Ventolin? A randomised, blinded, crossover study in New Zealand

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Abstract

Aim The effectiveness of the fully subsidised bronchodilator in New Zealand, Salamol®, has recently been questioned. We compared the efficacy of Salamol® and Ventolin® inhalers in relieving acute bronchospasm. We also tested the efficacy of partially used Salamol inhalers because of concerns that the device may become blocked during use.

Methods 12 asthmatic subjects were enrolled in this randomised, single-blind, 3-way crossover study. Subjects inhaled methacholine to produce a 20% fall in forced expiratory volume at 1 second (FEV$_1$) on 3 different days. Salbutamol was given post-bronchoconstriction as Ventolin, Salamol (new), or Salamol (used) in random order. Inhalations of 100, 100, and 200 mcg salbutamol were delivered at 5 minute intervals via spacer and FEV$_1$ was measured 5 minutes after each dose. The main outcome variable was the area under the salbutamol dose response curve.

Results There was no significant difference in the bronchodilator response to salbutamol whether delivered as Ventolin or Salamol (p=0.63). Furthermore, there was no difference in bronchodilator response between used Salamol inhalers and new Salamol inhalers (p=0.60) or between used Salamol inhalers and Ventolin (p=0.08). The final FEV$_1$s at 15 minutes (after a total of 400mcg salbutamol) were also similar for the different inhalers.

Conclusions We found no evidence that either new or partially used Salamol inhalers are less effective at relieving acute bronchoconstriction than Ventolin.

Beta-agonists are the most effective bronchodilators for symptom relief in asthma. Ventolin® inhalers which contain salbutamol have been widely used for many years in New Zealand. However there are now a range of generic salbutamol inhalers available and Ventolin is no longer fully-funded by PHARMAC (New Zealand’s medication funding authority). Plans have been made to gradually replace it with a cheaper generic alternative, Salamol®. Studies have demonstrated equivalent bioavailability (in terms of post-dose plasma and urine concentration) and bronchodilation (in terms of post dose lung volumes) between Ventolin and Salamol in stable patients. However, since its introduction to New Zealand, anecdotal reports have centred on negative aspects of Salamol. Complaints include decreased therapeutic effect, inhaler blockage, and unpleasant taste.

Reti recently reported the experiences of 36 adults being switched from Ventolin to Salamol in general practice. Most of these were either unable to tolerate the new inhaler or experienced worse asthma control. Unfortunately, no objective measures...
of lung function or bronchodilator response were obtained and the findings depended largely on patient perceptions.

The interpretation of these data was controversial. Nevertheless the pharmacological efficacy of Salamol has been called into question. In an environment of overwhelmingly negative media publicity about Salamol, the study by Reti leaves the question of Salamol’s clinical effectiveness unanswered.

To shed more light on this issue, we compared the effectiveness of Salamol and Ventolin in relieving acute bronchoconstriction. Because there has been some concern that Salamol inhalers may become blocked during use, we further compared the effectiveness of new and partially used Salamol inhalers.

**Methods**

**Subjects**—Volunteers aged 21–64 years with mild to moderate asthma were recruited. All had bronchial hyper-responsiveness to methacholine (provocative dose causing a 20% fall in forced expiratory volume in one second (FEV₁) (PD₂₀) of less than 8 µmol. Subjects who had used oral corticosteroids in the previous 3 months were excluded, as were those using long acting beta-agonist inhalers and current or previous heavy cigarette smokers (> 5 pack years). All subjects provided written informed consent. Ethics approval for the study was granted by the Northern Y Regional Ethics Committee.

**Study design**—After abstaining from bronchodilators for at least 6 hours, the subjects inhaled methacholine to produce a 20% fall in FEV₁ on 3 different days. Salbutamol was than administered as Ventolin, Salamol (new), or Salamol (used) pressurised metered dose inhalers (MDI) via spacer (100 µg per actuation).

The subjects received a different inhaler on each of the 3 days and the order in which they received the inhalers was randomised by computer. The inhalers were concealed in a sock to maintain blinding of the subjects to which inhalers they were receiving.

Methacholine challenge was performed using a modified Yan technique. Baseline FEV₁ was the highest of 3 consistent measurements. Subjects then inhaled doubling doses of nebulised methacholine from 0.0073mg to 3.728mg from a dosimeter. FEV₁ was measured 1 minute after each dose. Once the FEV₁ had fallen by ≥ 20% from baseline, methacholine challenge was stopped. The PD₂₀ (cumulative dose) was calculated by linear interpolation.

Salbutamol (Ventolin® marketed by GlaxoSmithKline, Auckland, New Zealand; and Salamol® marketed by Airflow, Wellington, New Zealand) 100µg, 100µg, and 200µg via metered dose inhaler and volumatic spacer were given at 0, 5, and 10 minutes after methacholine challenge respectively. The FEV₁ was measured 5 minutes after each dose of salbutamol, giving a total response time of 15 minutes.

Two different Salamol MDIs were used by each subject—one new (i.e. clean and unblocked) and one used (i.e. after 100 actuations in increments of 10, at least one week previously and not washed).

**Measurements**—The main outcome measurement was the area under the salbutamol response curve (AUC), expressed as FEV₁ gained in litres after methacholine induced fall. The final FEV₁s after 15 minutes (cumulative dose 400µg salbutamol) were also compared.

**Statistics**—The AUCs for each treatment were analysed by ANOVA. Specific comparisons between treatment arms [e.g. Ventolin and Salamol (new)] were made using paired t-tests. The sample size was calculated from previous investigations to provide 90% power to detect a 30% difference in AUC with a significance of 0.05.
Results

Thirteen subjects were recruited. One subject (participant 3) withdrew after the first study day due to personal reasons. Twelve subjects (3 males) completed the study protocol. Baseline data on the subjects are presented in Table 1.

Table 1. Baseline data on subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Dose of inhaled Steroids (mcg)*</th>
<th>Baseline FEV₁ (L)</th>
<th>FEV₁ (% Predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>female</td>
<td>0</td>
<td>2.48</td>
<td>89%</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>female</td>
<td>0</td>
<td>3.06</td>
<td>95%</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>female</td>
<td>1000</td>
<td>2.85</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>female</td>
<td>0</td>
<td>3.37</td>
<td>104%</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>female</td>
<td>400</td>
<td>2.08</td>
<td>94%</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>female</td>
<td>400</td>
<td>2.87</td>
<td>95%</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>female</td>
<td>800</td>
<td>1.77</td>
<td>55%</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>male</td>
<td>300</td>
<td>1.38</td>
<td>40%</td>
</tr>
<tr>
<td>10</td>
<td>44</td>
<td>female</td>
<td>800</td>
<td>1.83</td>
<td>77%</td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>male</td>
<td>0</td>
<td>6.21</td>
<td>113%</td>
</tr>
<tr>
<td>12</td>
<td>49</td>
<td>female</td>
<td>0</td>
<td>2.50</td>
<td>96%</td>
</tr>
<tr>
<td>13</td>
<td>58</td>
<td>male</td>
<td>800</td>
<td>1.80</td>
<td>58%</td>
</tr>
</tbody>
</table>

*budesonide equivalent (beclomethasone = budesonide = 2 x fluticasone)

Table 2. Lung function pre/post methacholine challenge

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Ventolin (L) (95%CI)</th>
<th>Salamol(New) (L) (95% CI)</th>
<th>Salamol(Used) (L) (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Baseline FEV₁</td>
<td>2.50 (1.9-3.1)</td>
<td>2.48 (1.9-3.0)</td>
<td>2.47 (1.9-3.0)</td>
<td>0.79</td>
</tr>
<tr>
<td>Mean Post-MC* FEV₁</td>
<td>1.94 (1.5-2.4)</td>
<td>1.88 (1.4-2.3)</td>
<td>1.89 (1.4-2.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>GeoMean PD₂₀ (mg)</td>
<td>0.14</td>
<td>0.14</td>
<td>0.18</td>
<td>0.60</td>
</tr>
<tr>
<td>Mean FEV₁ post Salbutamol (cumulative)</td>
<td>2.24</td>
<td>2.22</td>
<td>2.17</td>
<td>0.51</td>
</tr>
<tr>
<td>100µg (L)</td>
<td>2.37</td>
<td>2.38</td>
<td>2.35</td>
<td>0.86</td>
</tr>
<tr>
<td>200µg (L)</td>
<td>2.50</td>
<td>2.50</td>
<td>2.45</td>
<td>0.57</td>
</tr>
<tr>
<td>Mean AUC**(L/min) (95% CI)</td>
<td>6.8 (5.4-8.2)</td>
<td>6.8 (5.4-8.2)</td>
<td>6.7 (5.3-8.1)</td>
<td>0.63***</td>
</tr>
</tbody>
</table>

*MC = Methacholine Challenge; **AUC = Area under the salbutamol response curve; ***Paired t-tests: p = 0.60 (Ventolin vs Salamol New); p = 0.08 (Ventolin vs Salamol Used)
Figure 1. Mean FEV₁ response curve. Data are expressed as a percentage of the baseline (pre-methacholine) FEV₁.

Figure 2. Areas under the salbutamol dose response curves for each individual.

There were no significant differences in mean baseline FEV₁ (p=0.71) geometric mean PD_{20} (p=0.60) or in the percentage fall in FEV₁ induced by methacholine (p=0.33) between the treatment arms.
Mean FEV$_1$ response curves for each treatment are shown in Figure 1. There was no significant difference in the AUC between the three treatment arms (ANOVA, p=0.63). There was also no difference in the mean AUC comparing Ventolin and Salamol (p=0.79) nor between Salamol (new) and Salamol (used) inhalers (p=0.60). A small trend favouring the Ventolin treatment group was observed when compared with Salamol (used) inhalers but this was not statistically significant (p=0.084).

The final FEV$_1$s after 15 minutes (i.e. after a cumulative dose of salbutamol 400 µg) were also not different between treatments (Table 2).

**Discussion**

We found no difference in the efficacy of either new or partially used Salamol inhalers in relieving bronchoconstriction compared to Ventolin. These findings suggest that reports of deterioration in asthma stability on switching to Salamol and ineffectiveness of Salamol inhalers are unlikely to be due to a lack of bronchodilator efficacy.

Our findings are consistent with previous studies of the bioavailability of salbutamol from Salamol inhalers. They are also compatible with previous reports of the equivalence of Salamol in stable asthma. However, studies in stable asthma can be misleading since full bronchodilation can be achieved with small doses of β-agonists. In practice, β-agonists are used to relieve acute bronchoconstriction. Previous studies indicate that the “challenge-rescue” model that we have used is far better at identifying differences in bronchodilator efficacy than bronchodilator response tests in stable asthma and has been used in several studies to assess tolerance to long and short acting β-agonist inhalers. The fact that we found virtually identical responses to Salamol and Ventolin using this technique suggests that it is unlikely that clinically meaningful differences between the effectiveness of these inhalers exist.

There may be other reasons why patients might prefer Ventolin to Salamol. These include familiarity with the inhaler and the taste of the aerosol. In our study, several patients commented on the unpleasant taste of the Salamol, even though this had been given via spacer from a blinded inhaler. It is also possible that the other components of the aerosol have an adverse effect on asthma control over a longer term. We have no data on this and, although it seems unlikely, this possibility cannot be excluded.

There has also been widespread concern that the Salamol MDI is more prone to blockage than the Ventolin MDI (due to the smaller dispensing port of Salamol MDI). New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has therefore recommended that Salamol inhalers are cleaned regularly. However, many patients will forget to do this and may be unable to do this during an acute exacerbation. We therefore tested partially used (more than 100 actuations) Salamol inhalers which had not been cleaned. There was no evidence that any of these inhalers were less effective (Figure 2). Hence, inhaler blockage did not appear to be a problem in any of the 12 used Salamol inhalers used in this study. Although we cannot exclude the possibility that occasional inhalers block, this seems very unlikely to explain the widespread dissatisfaction with Salamol inhalers in the study by Reti.

Based on previous studies, this study was powered to detect a 30% difference in the area under the bronchodilator response curve. The actual differences in AUC that we detected were 0.6% lower with new Salamol inhalers and 2% lower with used
Salamol inhalers. Neither of these differences was statistically significant. We cannot exclude the possibility that there is a small difference between Salamol and Ventolin inhalers; however our findings indicate that any such difference is unlikely to be clinically relevant.

There are a number of limitations to this study. The study was single (rather than double) blind, and even though the inhalers were concealed from the subjects, some could taste a difference and may have guessed which inhaler was being used. Using an objective outcome measure (FEV\textsubscript{1}) will have minimised any bias due to this possible loss of blinding. We also limited the dose-response time to 15 minutes because previous studies indicate that the spontaneous recovery from methacholine challenge is minimal within this time.\textsuperscript{9} It is unlikely that a longer period of observation would have revealed differences between the inhalers because salbutamol is a fast-acting bronchodilator and most subjects fully recovered within the observation period (Figure 1). Perhaps the most important limitation is that Ventolin and Salamol were administered via a spacer. Although this is the recommended method for relieving acute bronchospasm,\textsuperscript{1} in practice many patients use their inhalers without a spacer. It is possible that there are greater differences in the delivery of salbutamol to the airways and therefore in the effectiveness of Salamol and Ventolin when a spacer is not used. To investigate this would require a further study.

In summary, we have found no difference in the ability of Salamol and Ventolin to relieve acute bronchoconstriction. We also found no evidence of inhaler blockage reducing the effectiveness of Salamol. It is unlikely that the reported patient preference for Ventolin over Salamol are due to Salamol being a less effective bronchodilator. There are many reasons why patients may prefer to continue with their usual inhaler. However, patients can be reassured that the fully funded generic alternative is an equally effective bronchodilator.

Competing interests: None

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