Dose equivalence and bronchoprotective effects of salmeterol and salbutamol in asthma

Matthew A Higham, Abdelmonen M Sharara, Peter Wilson, Richard J Jenkins, G Alastair Glendenning, Philip W Ind

Abstract

Background — Salmeterol is the most widely prescribed short acting β₂ agonist and salmeterol is the first long acting inhaled β₂ agonist. The dose equivalence of salmeterol and salbutamol is disputed. Estimates of weight-for-weight dose ratio have ranged from 1:2 to 1:16. A study was undertaken to clarify the true dose ratio.

Methods — The bronchoprotection afforded against repeated methacholine challenge by inhaled salmeterol 25 µg and 100 µg and salbutamol 100 µg and 400 µg was compared in a randomised, double blind, placebo controlled, crossover trial. Subjects were 16 stable asthmatics with a baseline forced expiratory volume in one second (FEV₁) of ≥65% predicted, screen- ing concentration provoking a fall in FEV₁ of 20% (PC₂₀FEV₁) of ≤8 mg/ml, and a shift in PC₂₀FEV₁ of more than two doubling concentration steps following inhalation of salbutamol 400 µg. On five separate occasions subjects underwent methacholine challenge before and 30 and 120 minutes after drug administration. PD₁₀₀FEV₁ was calculated for each challenge. FEV₁ at 90 minutes after drug administration was also recorded.

Results — Bronchoprotection afforded by salmeterol was increased at 120 minutes compared with 30 minutes and protection by salbutamol was decreased. Protection by both doses of salmeterol was similar to salbutamol 100 µg at 30 minutes but significantly greater at 120 minutes. FEV₁ at 90 minutes was significantly greater after salmeterol 100 µg than after placebo, but there were no other significant differences between treatments. Maximal observed protection was equivalent for salmeterol 100 µg and salbutamol 400 µg.

Conclusions — The data are compatible with a weight-for-weight dose ratio for salmeterol:salbutamol of ≤1:4.

(Thorax 1997;52:975–980)

Keywords: salmeterol, salbutamol, dose equivalence.

Inhaled β₂ adrenoceptor agonists are the most effective bronchodilators and are widely utilised for the relief and prophylaxis of bronchocstriction in asthma. Until recently all available β₂ agonists had short durations of action. Salmeterol xinafoate is a recently introduced long acting inhaled selective β₂ adrenoceptor agonist which produces dose-dependent bronchodilatation, reduction in diurnal variation in peak expiratory flow, improvement in daytime and nocturnal symptoms, reduction in requirement for a short acting bronchodilator, and increased quality of life in asthmatic patients. Bronchodilatation and protection against non-specific bronchial challenge with histamine or methacholine are maintained for at least 12 hours after a single dose of salmeterol compared with 4–6 hours after salbutamol.

Salmeterol and salbutamol have similar β₂ receptor selectivity but dose equivalence is disputed, estimates of the weight-for-weight dose ratio ranging from 1:2 to 1:16 in single dose studies. In the light of continuing debate regarding a possible association between the use of β₂ agonists and increasing asthma morbidity and mortality worldwide and concern about relative potencies of different agents, it is important that the relative potencies of these two drugs be defined.

Increased responsiveness to non-specific bronchoconstrictor agents is a characteristic feature of clinical asthma and inhaled histamine or methacholine bronchoprovocation tests are commonly used in diagnosis in patients who present with vague or atypical symptoms. The aim of this placebo controlled study was to compare the potency of salmeterol and salbutamol in asthmatic subjects by measurement of the protection afforded by salmeterol 25 µg and 100 µg and salbutamol 100 µg and 400 µg against repeated methacholine challenge. The design is a model for multidose comparison of inhaled bronchodilator drugs.

Methods

SUBJECTS

Sixteen stable mild asthmatic subjects (seven men) of mean age 29 (range 22–42) years were studied (table 1). Three were smokers and one was an ex-smoker. Subjects were either members of hospital or medical school staff or patients recruited from outpatient clinics. All had a diagnosis of asthma as defined according to American Thoracic Society criteria. Mean time (range) since diagnosis was 17 (1–38) years and mean (SD) baseline forced expiratory volume in one second (FEV₁) was 101.2 (14.5)% predicted. Nine subjects used inhaled salbutamol as required, one inhaled terbutaline as required, and three inhaled salbutamol as required plus an inhaled glucocorticosteroid regularly. Three subjects were not currently taking any asthma medication. No subject was using salmeterol prior to the study. No subject had had a recent respiratory tract infection nor...
The study was of a randomised, crossover, formed according to American Thoracic So-
merseth Hospital Research ethics committee
Postgraduate Medical School and Ham-

Table 1 Characteristics of subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Baseline FEV1 (% predicted)</th>
<th>Screening PD20 (μmol)</th>
<th>Asthma history (years)</th>
<th>Smoking status</th>
<th>Asthma medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>34</td>
<td>166</td>
<td>90.9</td>
<td>0.68</td>
<td>33</td>
<td>N</td>
<td>SALB, BDP</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>24</td>
<td>168</td>
<td>107.3</td>
<td>0.96</td>
<td>2</td>
<td>S</td>
<td>SALB</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>22</td>
<td>168</td>
<td>102.9</td>
<td>1.05</td>
<td>8</td>
<td>S</td>
<td>SALB</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>26</td>
<td>159</td>
<td>87.9</td>
<td>1.26</td>
<td>1</td>
<td>N</td>
<td>SALB</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>23</td>
<td>165</td>
<td>119.6</td>
<td>2.87</td>
<td>10</td>
<td>N</td>
<td>TERB</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>31</td>
<td>166</td>
<td>123.3</td>
<td>0.20</td>
<td>5</td>
<td>N</td>
<td>SALB</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>25</td>
<td>181</td>
<td>116.1</td>
<td>1.24</td>
<td>15</td>
<td>N</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>29</td>
<td>185</td>
<td>91.0</td>
<td>0.65</td>
<td>26</td>
<td>N</td>
<td>SALB, BUD</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>174</td>
<td>93.6</td>
<td>0.54</td>
<td>32</td>
<td>X</td>
<td>S</td>
<td>SALB</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>32</td>
<td>181</td>
<td>80.0</td>
<td>2.80</td>
<td>10</td>
<td>N</td>
<td>SALB</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>23</td>
<td>179</td>
<td>94.6</td>
<td>0.99</td>
<td>22</td>
<td>N</td>
<td>SALB</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>32</td>
<td>188</td>
<td>117.7</td>
<td>1.75</td>
<td>20</td>
<td>S</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>37</td>
<td>174</td>
<td>111.0</td>
<td>0.16</td>
<td>30</td>
<td>N</td>
<td>SALB</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>21</td>
<td>161</td>
<td>96.6</td>
<td>1.59</td>
<td>8</td>
<td>S</td>
<td>SALB, BDP</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>30</td>
<td>154</td>
<td>110.6</td>
<td>0.20</td>
<td>8</td>
<td>N</td>
<td>SALB</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>42</td>
<td>178</td>
<td>73.9</td>
<td>0.10</td>
<td>38</td>
<td>N</td>
<td>None</td>
</tr>
</tbody>
</table>

N = non-smoker; S = smoker; X = ex-smoker; SALB = salbutamol; TERB = terbutaline; BDP = beclometasone 500 μg bd; BUD = budesonide 200 μg bd.

an exacerbation of asthma in the previous four weeks. None had been admitted to hospital for an exacerbation of asthma in the previous 12 months. The study was approved by the Royal Postgraduate Medical School and Ham-

STUDY DESIGN

The study was of a randomised, crossover, double blind, double dummy design. Subjects attended the laboratory for a screening visit and five study visits at the same time of day, with a washout period of at least three days between each attendance. Short acting β2-agonists were discontinued for at least six hours before each attendance. Subjects were also asked to avoid tea and coffee for the same period because of the possible bronchodilator effects of caffeine. At screening a medical history was taken and methacholine challenge was performed. Subjects participated in the study if they had a provocative concentration of methacholine causing a 20% fall in FEV1 (PC20FEV1) of ≤8 mg/ml and a shift in PC20FEV1 of more than two doubling concentration steps 30 minutes after inhalation of salbutamol 400 μg, while remaining ≤64 mg/ml. Baseline FEV1 at each study visit was required to be ≥65% of the predicted value and to not deviate by more than 15% from the screening value. Baseline PC20FEV1 at each visit was required to be within two concentration steps lower or one higher than the screening value, and ≤8 mg/ml. If these criteria were not met an appointment was made for reattendance on another day.

On each study day baseline bronchial challenge with methacholine was performed. One hour after commencing the challenge subjects inhaled the study drug (salmeterol 25 μg or 100 μg, salbutamol 100 μg or 400 μg, or placebo). This was administered in a randomised, double blind, double dummy fashion. Further methacholine challenges were performed 30 and 120 minutes following drug administration. In addition, FEV1 was measured 90 minutes after dosing. At each visit subjects inhaled salbutamol 400 μg im-

SPIROMETRY, DRUG DELIVERY AND METHACHOLINE CHALLENGE

Spirometric measurements were made using a dry wedge bellows spirometer (Vitalograph, Vitalograph Ltd, Buckingham, UK) and performed according to American Thoracic Society guidelines. The highest of three technically acceptable measurements from a maximum of eight attempts was re-
corded. The two largest values from each set of measurements were required to be re-
producible to within 5%. Study medication (supplied by Glaxo Group Research, Greenford, Middlesex, UK) was de-

In order to abbreviate the challenge procedure, placebo). This was administered in a ran-

Further methacholine challenges were performed 30 and 120 minutes following drug administration. In addition, FEV1 was measured 90 minutes after dosing. At each visit subjects inhaled salbutamol 400 μg im-

mediately after the final challenge to reverse bronchoconstriction, and were allowed to leave when their FEV1 had returned to at least 80% of its baseline value.
Screening or at 0.0625 mg/ml, whichever was the higher. As a safety precaution, salbutamol by nebuliser was always immediately available for rapid reversal of bronchoconstriction if required.

**Data Analysis**

Means were adjusted for baseline patient and treatment. PD$_{20}$FEV$_1$ values for each challenge were obtained by linear interpolation from the cumulative log dose-response curve for that challenge. For PC$_{20}$FEV$_1$ values greater than 128 mg/ml a value of 130 mg/ml was assigned. All the data were then logged and analysed parametrically. The pre-dosing PD$_{20}$FEV$_1$ and the nature of the crossover design were taken into account in the analysis. Carry over, period and sequence effects were also investigated. The slopes of the FEV$_1$ changes measured during each challenge were analysed parametrically.

**Results**

Methacholine challenges were generally well tolerated, although subject no. 6 became uncomfortable and required 2.5 mg nebulised salbutamol for reversal of bronchoconstriction after the 120 minute challenge following salmeterol 25 µg. Adverse events considered to be related to study medication were tremor and headache in two different subjects, both after salbutamol 400 µg. These side effects are consistent with the known pharmacology of β$_2$ adrenoceptor agonists. Four subjects were required to attend extra study visits because of changes in baseline methacholine responsiveness – two subjects on one occasion, one on two occasions, and one on four occasions.

FEV$_1$

The effects of the different treatments on FEV$_1$ are shown in table 2. Tests for carry over and two-factor interactions with treatment were non-significant.

At 30 minutes after medication, prior to second bronchial challenge, mean FEV$_1$ was reduced after placebo (due to persistent bronchoconstriction following baseline methacholine challenge and possible diurnal variation) but increased after salmeterol 100 µg, salbutamol 100 µg, and salbutamol 400 µg. The absolute change in FEV$_1$ from baseline was significant in favour of all active treatments when compared with placebo (p≤0.001). The increase in FEV$_1$ after salbutamol 400 µg was significantly greater than after salmeterol 25 µg (absolute difference = 0.24 l (95% CI 0.10 to 0.38), p = 0.001). There were no other significant differences between treatments.

The lowest FEV$_1$ achieved during the 30 minute methacholine challenge did not differ significantly on any of the study days. On all treatment days mean FEV$_1$ 90 minutes after dosing was reduced compared with the baseline value due to the preceding methacholine challenge, but further recovery occurred by 120 minutes. There was no significant difference between study treatments other than a significantly smaller reduction in FEV$_1$ after salmeterol 100 µg than after placebo (absolute difference = 0.31 l (95% CI 0.12 to 0.50, p = 0.002).

The mean FEV$_1$ 120 minutes after salmeterol 100 µg was increased compared with the baseline value whereas it was reduced for all other treatments. However, all active treatments showed a significantly smaller reduction in FEV$_1$ than placebo (p≤0.011). The effect on FEV$_1$ was significantly greater after salmeterol 100 µg than after salmeterol 25 µg (absolute difference 0.16 l (95% CI 0.02 to 0.31), p = 0.028), salbutamol 100 µg (absolute difference 0.18 l (95% CI 0.04 to 0.32, p = 0.015), and salbutamol 400 µg (absolute difference 0.16 l (95% CI 0.02 to 0.31), p = 0.027). There were no other significant differences between treatments.

**Methacholine Challenge PD$_{20}$FEV$_1$**

The baseline geometric mean dose of methacholine causing a 20% reduction in FEV$_1$ (PD$_{20}$FEV$_1$) did not differ significantly between different treatment days. PD$_{20}$FEV$_1$ 30 and 120 minutes after dosing are shown in fig 1. All active treatments offered significantly better protection against methacholine-induced bronchoconstriction than placebo at 30 minutes (p<0.001) and at 120 minutes (p<0.001). Tests for carry over and two-factor interactions with treatment were found to be non-significant for both challenges. The results are shown in fig 2 and table 3 as doubling doses related to placebo response. Statistical analyses of treat-
7.00

Figure 2 Individual PD20 FEV1 data expressed as doubling doses of methacholine related to placebo response.

Table 3 Mean (SE) PD20 FEV1 expressed as doubling doses of methacholine related to placebo response

<table>
<thead>
<tr>
<th>Treatment/placebo</th>
<th>Ratio</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol 25 µg</td>
<td>3.9</td>
<td>&lt;0.001</td>
<td>2.5 to 6.2</td>
</tr>
<tr>
<td>Salmeterol 100 µg</td>
<td>6.9</td>
<td>&lt;0.001</td>
<td>4.4 to 10.8</td>
</tr>
<tr>
<td>Salbutamol 25 µg</td>
<td>1.8</td>
<td>0.017</td>
<td>1.1 to 2.8</td>
</tr>
<tr>
<td>Salbutamol 100 µg</td>
<td>1.1</td>
<td>&lt;0.001</td>
<td>0.59 to 2.0</td>
</tr>
<tr>
<td>Salmeterol 25 µg</td>
<td>1.3</td>
<td>0.059</td>
<td>0.6 to 2.0</td>
</tr>
<tr>
<td>Salmeterol 100 µg</td>
<td>3.4</td>
<td>0.005</td>
<td>1.2 to 3.1</td>
</tr>
<tr>
<td>Salmeterol 25 µg</td>
<td>1.8</td>
<td>&lt;0.001</td>
<td>1.4 to 2.8</td>
</tr>
<tr>
<td>Salmeterol 100 µg</td>
<td>6.9</td>
<td>&lt;0.001</td>
<td>2.5 to 7.0</td>
</tr>
</tbody>
</table>

Table 4 Geometric mean PD20 FEV1 data at 30 and 120 minutes expressed as ratios between different treatments

<table>
<thead>
<tr>
<th>Treatment/salbutamol 25 µg</th>
<th>Ratio</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol 25 µg 25 µg</td>
<td>5.7</td>
<td>&lt;0.001</td>
<td>3.8 to 8.6</td>
</tr>
<tr>
<td>Salmeterol 100 µg 25 µg</td>
<td>9.3</td>
<td>&lt;0.001</td>
<td>6.1 to 14.1</td>
</tr>
<tr>
<td>Salbutamol 25 µg 25 µg</td>
<td>2.5</td>
<td>&lt;0.001</td>
<td>1.7 to 3.9</td>
</tr>
<tr>
<td>Salbutamol 100 µg 25 µg</td>
<td>5.2</td>
<td>&lt;0.001</td>
<td>3.4 to 7.9</td>
</tr>
</tbody>
</table>

Discussion

We have compared salmeterol 25 µg and 100 µg and salbutamol 100 µg and 400 µg in terms of bronchoprotective effect against repeated methacholine challenge in order to estimate dose equivalence in subjects with mild stable asthma. Maximal observed bronchoprotection
was equivalent for salmeterol 100 μg and salbutamol 400 μg but was significantly greater for salmeterol 25 μg than salbutamol 100 μg (p = 0.01). Salmeterol 25 μg was equivalent to salbutamol 100 μg at 30 minutes but significantly more effective at 120 minutes. At 30 minutes salmeterol 100 μg was less effective than salbutamol 400 μg while at 120 minutes it was significantly more effective. The magnitude of protection due to salmeterol increased over the course of 120 minutes, while protection afforded by salbutamol decreased. This is consistent with the known onset and duration of action of these drugs. It is compatible with previous studies showing a slower onset of action of salmeterol and a longer duration of action than salbutamol in human airways in vivo and in vitro.

Inevitably there are some limitations to a study of this nature. Only a relatively small number of subjects was studied but the study design ensured that the pre-drug methacholine challenge was reproducible by determination of baseline on each treatment day. Subjects were clinically stable throughout the duration of the study. Baseline FEV1 did not differ significantly between study days and was comparable to screening values, so the observed changes in FEV1 and PD20FEV1 can confidently be attributed to drug and dose differences. The study methodology was adequate to distinguish a fourfold difference in dose for salbutamol. Methacholine challenge at 30 minutes and at 120 minutes could have been performed on different days to avoid possible cumulative bronchoconstriction, but such a design would be impractical and has not been adopted by others. It would be similarly onerous to increase the number of doses of each drug studied to construct full log dose-response curves.

No study has previously reported the bronchoprotective effects of salmeterol at exactly these doses and time points but our results are in line with those of other workers. Cheung and coworkers reported an acute protective effect of salmeterol 50 μg with a 2.3-fold doubling dose increase in P20aFEV1 at one hour, whereas Derom et al found salmeterol 50 μg equivalent to salbutamol 200 μg with a 1.9-fold doubling dose increase in P20aFEV1 at one hour. Gongora et al compared the protective effects of salmeterol and salbutamol, delivered by metered dose inhaler, against histamine challenge in a placebo controlled study. They reported an increase of 2.7 doubling doses of histamine one hour after salmeterol 50 μg compared with 1.8 after salbutamol 200 μg. These results are very comparable to our own. Our time points were chosen to obtain comparable bronchodilator effects of the two drugs, bearing in mind their different time courses of action.

It should be noted that bronchoprotective effects may not necessarily be identical to bronchodilator effects. However, it would be difficult to compare bronchodilator effects of the higher doses of the two β2 agonists used due to the shape of the dose-response curve and the tendency of FEV1 to plateau below maximal therapeutic dosage so that increasing doses cannot be discriminated.

In the present study there was a trend for salmeterol 100 μg to exhibit a greater bronchodilator effect than salmeterol 25 μg after baseline methacholine challenge, as shown by FEV1 at 90 and 120 minutes, though this did not achieve statistical significance. There was a trend to greater protection after salbutamol 400 μg than after salmeterol 100 μg, although this did not achieve statistical significance. We cannot exclude the possibility of a plateau bronchoprotective effect at the higher dose of salbutamol, suggesting that the relative potency ratio for salmeterol to salbutamol might be slightly less than 1:4. Comparison of the effects of β2 adrenoceptor agonists on methacholine responsiveness therefore offers a sensitive, convenient and reproducible method for comparing potency of drugs of this class, and has been recommended as a method for determining equivalence of inhaled medications.

In vitro studies suggest a fourfold greater affinity of salmeterol for β2 receptors and that salmeterol is 2–15 times more potent than salbutamol. Previous single dose studies in vivo in humans have suggested a dose equivalence of salmeterol compared with salbutamol of 2–16, but these studies have largely relied on change in FEV1. As discussed above, this is an insensitive method of estimating relative potency. A more comprehensive study compared cumulative doses of salbutamol with three single doses of salmeterol. Heart rate, plasma potassium, QTc interval, and tremor were examined in vitro. This study showed a wide range of dose equivalence values (3–13) depending on which parameter was analysed. Our data are compatible with a weight-for-weight dose ratio for salmeterol to salbutamol of ≤1:4 and a molar dose ratio of ≤1:3:8.

This is the first study to compare directly protection afforded by two doses of salmeterol and two doses of salbutamol. It agrees with the large multicentre clinical studies on which the clinically recommended therapeutic doses of salmeterol were based. The data show that salmeterol offers a new perspective for the treatment of asthma.


Dose equivalence and bronchoprotective effects of salmeterol and salbutamol in asthma.

M A Higham, A M Sharara, P Wilson, R J Jenkins, G A Glendenning and P W Ind

Thorax 1997 52: 975-980
doi: 10.1136/thx.52.11.975

Updated information and services can be found at:
http://thorax.bmj.com/content/52/11/975

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Drugs: respiratory system (526)
- Airway biology (1100)
- Asthma (1782)
- Lung function (773)
- Screening (epidemiology) (366)
- Screening (public health) (366)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/