A comparative study of a new selective $\beta_2$-adrenoceptor agonist, procaterol and salbutamol in asthma

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1 The effects of single oral doses of a new selective $\beta_2$-adrenoceptor agonist procaterol (0.05 mg and 0.1 mg) and salbutamol (4 mg) on ventilatory function, were compared in 24 asthmatic patients.
2 A bronchodilator effect of similar duration and magnitude followed all three treatments with no evidence of a dose-related response in the case of procaterol.
3 There was no significant difference in blood pressure or heart rate responses or pattern of unwanted effects.
4 We conclude that procaterol and salbutamol are clinically similar with oral dosing and that the maximum effective dose of procaterol is not greater than 0.05 mg.

Keywords procaterol salbutamol asthma $\beta_2$-adrenoceptor agonist

Introduction

Procaterol, 5-(hydroxy-2-isopropylaminobutyl)-8-hydrocarbostyril hydrochloride hemihydrate (Figure 1), is a new $\beta_2$-selective adrenoceptor agonist, which has been under investigation in the United States and clinical studies indicate that it is an effective bronchodilator in asthmatic patients (Zanetti et al., 1982). Both in vitro and in vivo animal studies (Himori & Tairi, 1977; Youichi & Yabuuchi, 1977; Yabuuchi, 1977) suggest that procaterol is not only more potent but also has a longer duration of action than salbutamol.

The purpose of the present study was to compare the cardiorespiratory activity, duration of action and pattern of unwanted effects of procaterol and salbutamol in asthmatics.

![Figure 1](image-url) Structural formula of (a) salbutamol and (b) procaterol.

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Methods

This was a randomised double-blind cross over study comparing oral doses of procaterol (0.05 and 0.1 mg) and salbutamol (4 mg). Each patient received the treatment in random order with at least 24 h, and not more than 7 days between exposures. A double dummy was used to ensure that the study was double-blind.

Twenty four patients aged 18–61 years with bronchial asthma comprised the study group. Diagnosis of bronchial asthma was based on medical history, physical signs and a demonstration of at least 20% improvement in FEV₁ after inhalation of 240 μg isoprenaline aerosol.

Patients with moderate or severe hypertension (diastolic blood pressure greater than 110 mm Hg), ischaemic heart disease, disorders of cardiac rhythm and/or conduction, thyrotoxicosis, diabetes mellitus, hepatic or renal disease and patients who were pregnant were excluded from the study. Informed consent was obtained from all subjects and the protocol was approved by the Hospital Ethics Committee.

No other bronchodilator (β₂-adrenoceptor stimulant, xanthine derivative or anticholinergic agent) was permitted during the study, or for 6 h (inhalers) or 12 h (oral) before commencing control readings on each study day. Other anti-asthmatic medication such as corticosteroids, disodium cromoglycate, were permitted provided the daily doses were kept constant throughout the study. During the 10 h study period patients were not allowed to consume tea, coffee, lucozade, and refrained from smoking.

Following a light breakfast control measurements of supine and standing blood pressure and heart rate were taken followed by forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC). The patient then received study medication consisting of three tablets, (two placebo and one active). Blood pressure, heart rate, FEV₁ and FVC were measured at 15, 30, 45 min and 1, 2, 3, 4, 6, 8, 10 h thereafter. In four subjects the observations were made only up to 8 h. An ECG was taken between the 6 and 8 h observation points. At the end of the study period patients were given a 2 min inhalation of 10 mg of isoprenaline sulphate to assess maximal bronchodilation. This was administered as 1 ml of isoprenaline sulphate 1% (Aleudria) diluted with 1 ml of normal saline. Subsequently, heart rate, blood pressure and FEV₁ were measured at 5 min intervals for 30 min.

Blood pressure was measured by standard sphygmomanometer, heart rate from radial pulse and FEV₁ and FVC were estimated using a Vitalograph. Details of unwanted effects were elicited by open questioning of the patient at each measurement time; patients were asked if they had any side effects.

Mean differences from baseline were plotted. Differences between pre- and post-isoprenaline inhalation responses were compared using analysis of covariance. For FEV₁ and FVC analysis of covariance was used to compare maximum increases from baseline.

Results

One patient failed to complete the study. He was withdrawn due to unwanted effects, after the first treatment of procaterol 0.05 mg (see below).

Baseline FEV₁ (mean ± s.e. mean) were procaterol (0.05 mg) 1.22 ± 0.09 l, procaterol (0.1 mg) 1.31 ± 0.11 l, salbutamol 1.16 ± 0.11 l. An increase in FEV₁ with all treatments was observed (Figure 2). In all cases this reached a maximum 2–4 h after administration and

![Figure 2](image-url)  
**Figure 2** Increase in FEV₁ after oral doses of procaterol 0.05 mg (O--O), procaterol 0.1 mg (●--●) and salbutamol (■--■). Values shown are the mean for 24 patients.
Procaterol and salbutamol in asthma

gradually returned towards baseline so that bronchodilatation was insignificant after 8 h. With every treatment the maximum percentage increase in FEV₁ exceeded 20%, the mean peak being 36%, 30% and 35% with procaterol 0.05 mg, 0.1 mg and salbutamol respectively. At 6 h after dosing the percentage increase in FEV₁ exceeded 15% in all cases. There was no difference in the magnitude or duration of the effects with treatment.

Baseline FVC (mean ± s.e. mean) values were procaterol (0.05 mg) 2.28 ± 0.03 l, procaterol (0.1 mg) 2.36 ± 0.03 l and salbutamol 2.13 ± 0.04 l). The change in FVC were quantitatively similar to those for FEV₁ (Figure 3).

Following isoprenaline sulphate a significant increase from pre-inhalation response was observed at each post-inhalation assessment with each treatment (P < 0.01). Maximum mean increase in FEV₁ with isoprenaline were 36%, 37%, 37% after procaterol 0.05 mg, 0.1 mg and salbutamol respectively. There was no significant difference between the peak responses after drug and isoprenaline sulphate inhalation.

Lying and standing systolic and diastolic (Figure 4) blood pressure decreased following procaterol 0.1 mg and salbutamol. Mean changes were less than 8 mm Hg and there was no overall difference in treatment response. Supine heart rate showed no significant change from baseline throughout the assessment period.

Unwanted effects and their incidence with each treatment are set out in Table I. There was no overall difference with each of the three treatments. However, headache occurred in 7/24 with low dose procaterol compared with three when salbutamol was taken. One patient was withdrawn after the first treatment (procaterol 0.05 mg) due to severe headache, nausea, vomiting and syncope occurring 9 h after drug ingestion. One patient had ST segment depression in leads II III and AVF and T wave flattening in AVL on day 1 and 2 of the trial (procaterol 0.05 mg and salbutamol respectively). The changes were not associated with symptoms and had returned to normal on the third trial day.

Discussion

In this study procaterol and salbutamol had equivalent effects on respiratory function. Both treatments resulted in an increase in FEV₁ greater than 30% with significant bronchodilator effect still evident following all treatments at 6 h. Peak effect occurred 2–4 h after treatment. There was no significant difference between the three treatments in magnitude or duration of bronchodilator response. Furthermore, there was no evidence of a dose related effect with procaterol so, presumably, the lower dose should be used clinically. However, this finding is at variance with that of Zanetti and colleagues (1982) who found a greater duration of bronchodilator action and a higher heart rate with 0.1 mg than with 0.05 mg. In the present study there was no significant differences in heart rate or blood pressure response following the three treat-

Figure 3 Increase in FVC after oral doses of procaterol 0.05 mg (○----○), procaterol 0.1 mg (●—●) and salbutamol (■—■). Values shown are the mean for 24 patients.
ments. As the study of Zanetti and colleagues (1982) was double-blind and placebo controlled it is difficult to reconcile the different results in the two studies.

Only one patient was withdrawn because of unwanted effects—nausea, vomiting and syncope following procaterol, 0.05 mg 9 h after drug administration. While emesis has been noted in animal toxicology studies, this episode occurring as it did, 9 h after ingestion of the drug, may not have been due to procaterol.

ST segment and T wave abnormalities have been well documented in patients on β-adrenoceptor agonists and have been attributed to greater synchronisation of atrial and ventricular repolarization respectively (Whitsett et al., 1981). The majority of unwanted effects such as tremor, headache and palpitations are those normally associated with β-adrenoceptor agonist. The overall incidence of unwanted effects was similar with the two drugs in this study. It is notable that seven of eight patients

Table 1 Unwanted effects related to treatment

<table>
<thead>
<tr>
<th>Unwanted effect</th>
<th>Procaterol 0.05 mg</th>
<th>Procaterol 0.1 mg</th>
<th>Salbutamol 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lightness</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiredness</td>
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</tr>
<tr>
<td>Chest tightness</td>
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</tr>
<tr>
<td>Burning sensation</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Strange dreams</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total number of reports</td>
<td>16</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Number of patients who reported unwanted effects</td>
<td>12</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Number of patients who received treatment</td>
<td>24</td>
<td>23</td>
<td>23</td>
</tr>
</tbody>
</table>
who experienced tremor had not been receiving oral β-adrenoceptor agonists whereas, of the fourteen patients who were receiving these only one encountered tremor. The decrease in these problems with continuing therapy is well recognised (Larsson, 1977).

We conclude that this study showed no significant difference between procaterol and salbutamol in cardiorespiratory activity, duration of action or incidence of unwanted effects. In fact the pattern of activity with the two drugs is strikingly similar.

References


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