Bronchial and cardiovascular responses to inhaled reproterol in asthmatics: a double-blind placebo controlled dose-response study

P. PATCHETT, S. M. PATCHETT & P. SHERWOOD BURGE

Department of Thoracic Medicine, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST

- 1 Reproterol is a synthetic selective β -adrenoceptor agonist with a xanthine side chain.
- 2 The bronchial and cardiovascular responses to inhaled reproterol were studied in 14 asthmatics. The study was placebo controlled and double-blind, comparing doubling doses of reproterol from 500 μ g–8 mg.
- 3 The peak improvement in FEV₁ showed a non-linear dose-response, with an initial plateau at the 1 mg dose producing a mean increase in FEV₁ of 17%, but significant further improvement at the 8 mg dose, producing a mean improvement of 29% in FEV₁.
- 4 The time taken for improvement in airways obstruction to start shortened with increasing doses.
- 5 The duration of bronchodilation was dose-dependent, with the 8 mg dose showing a significantly longer duration of action than the lower doses.
- 6 The time to drop below 75% of the maximum achieved bronchodilation was 125 min, and was independent of the dose.
- 7 There were no significant changes in pulse or blood pressure at any dose.
- 8 The study shows that reproterol is a well tolerated selective β_2 -adrenoceptor agonist whose duration of action and peak effect can be significantly increased by increasing the dose to 8 mg, without producing more unwanted effects.

Keywords reproterol asthma β_2 -adrenoceptor agonist

Introduction

Reproterol (β -phenylethylamine alkylxanthine, Bronchodil) is a synthetic selective β_2 -adrenoceptor agonist with a xanthine side chain (Habersang *et al.*, 1977). Human studies with both oral and intravenous reproterol consistently report a low frequency of both cardiovascular and subjective side effects (Zecevic *et al.*, 1977; Deiwitz, 1977; Bateman *et al.*, 1979). The drug was developed to try and produce a selective β_2 -adrenoceptor agonist whose metabolism was impaired by the addition of a large xanthine side chain. It is highly unlikely that the concentration of xanthine released is sufficient to have any clinical effect. A com-

parison of 4 mg salbutamol with 20 mg reproterol demonstrated a similar improvement in twice daily peak flow measurements with both drugs given by mouth three times daily for 4 weeks (Bateman *et al.*, 1979). A comparison of inhaled salbutamol 200 μ g with inhaled reproterol 1 mg showed lower peak values of FEV₁ following reproterol (Hendy & Burge, unpublished), suggesting that the standard 1 mg dose of inhaled reproterol was suboptimal for the regular treatment of asthma. We therefore set out to study the dose-response characteristics of inhaled reproterol in responsive asthmatics studied in their 'normal' state.

Correspondence: Dr P. S. Burge, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST.

Methods

Fourteen patients with bronchial asthma were studied. All suffered from chronic asthma and had not recently suffered from an acute exacerbation. There were nine men and five women with ages ranging from 22–64 years. All had a demonstrable 15% improvement in PEFR after the inhalation of 200 µg of salbutamol from a metered dose inhaler. During this study the improvement in peak flow between individuals varied from 20%–100%, individuals reaching 80%–115% of their predicted values. Patients were not studied if they were pregnant, if they were hypersensitive to theophyllines or if they were receiving oral corticosteroids, theophyllines or β_2 -adrenoceptor agonists. The subjects were asked to discontinue inhaled β_2 -adrenoceptor agonists at least 10 h before each day's study. Since we found it hard to find 'stable' asthmatics who were responsive to salbutamol we studied asthmatics with daily variable asthma, but only studied them on days when their starting FEV₁ was within 10% of all their other starting values.

The study began on each of at least 6 days between 09.30 and 10.00 h. Baseline pulse, blood pressure (using a standard sphygmomanometer), PEFR (Wright's Peak Flow Meter), FEV₁ and FVC (Vitalograph dry wedge spirometer) were recorded. Measurement of FEV₁ and FVC were continued until there were at least two satisfactory traces with the best two values within 100 ml of each other. At least three peak flow measurements were made, the best two to be within 20 l min⁻¹. On each occasion the best result was recorded. Following administration of the inhalers the same readings were repeated at 10 min intervals for 2 h and then at 20 min intervals for a further hour when measurements of FEV₁ and FVC were stopped. Measurements of PEFR, which had been made by the subjects themselves under supervision for the first 3 h, were continued unsupervised for a further 6 h.

On each day following taking the baseline readings the patients administered to themselves a total of 16 puffs from six separate pressurised inhalers. Each inhaler contained either propellant and flavouring alone or 500 µg of reproterol per actuation. The study was designed so that the daily doses of reproterol were 0, 500 µg, 1 mg, 2 mg, 4 mg or 8 mg. The dosages were randomised in order and administered double-blind from a total of 36 coded pressurised inhalers. Inhaler technique was standardised by supervision and advice including the use of a slow inhalation followed by breath holding for 10 s. Results of FEV₁ and peak flow were expressed as percent change from the starting value on the day of study. The mean values are

shown in the figures. The standard errors are shown in the tables.

Statistics

Comparisons were made appraised one-way, using paired *t*-tests.

Results

Comparability of baseline measurements

There were no significant differences between the baseline values for FEV₁ or peak flow on the six study days. The mean baseline values (s.e. mean) for peak flow was 375 (22), 382 (23), 381 (26), 367 (23), 375 (24) and 379 (23). The mean (s.e. mean) values of FEV₁ were 2.07 (0.18), 2.18 (0.18), 1.96 (0.23), 1.98 (0.18), 2.03 (0.17) and 2.05 (0.19).

Peak effect

The mean maximum values of FEV₁ following reproterol were reached between 100 and 120 min after dosing (Figure 1, Table 1). The rise in FEV₁ occurred more quickly following doses of 2 mg or greater. At the standard dose of 1 mg under 50% of the maximum improvement had occurred by 20 min. The maximum FEV₁ achieved was similar with doses between 500 µg and 2 mg. The improvement following 8 mg was significantly better than that achieved following doses of 2 mg or less ($P < 0.005$). The results following 4 mg were intermediate and on their own not significantly different from the 2 mg or 8 mg doses. The FEV₁ also increased following placebo, but in a different pattern with continuing improvement reaching a mean improvement of 11.4% at 3 h.

Figure 1 The FEV₁ response to inhaled reproterol, expressed as % change from baseline values.

Table 1 Percentage FEV₁ increase ($\pm$ s.e. mean) compared with the same six doses of reproterol over a 3 h period.

Time (min)	Dose of reproterol (mg)					
	0	0.5	1	2	4	8
10	-0.4 $\pm$ 1.9	6.7 $\pm$ 1.8	3.7 $\pm$ 1.9	9.8 $\pm$ 4.4**	12.6 $\pm$ 1.9*	20.0 $\pm$ 4.8***
20	0.8 $\pm$ 1.2	7.5 $\pm$ 1.8*	6.2 $\pm$ 2.4	11.5 $\pm$ 6.0*	17.0 $\pm$ 1.9**	23.1 $\pm$ 5.8***
40	2.2 $\pm$ 1.9	13.0 $\pm$ 3.0**	13.6 $\pm$ 2.8*	15.3 $\pm$ 4.1**	18.5 $\pm$ 1.7**	27.1 $\pm$ 6.4***
60	4.0 $\pm$ 1.4	14.9 $\pm$ 3.0	14.3 $\pm$ 2.9	17.0 $\pm$ 4.1***	19.8 $\pm$ 1.9***	28.1 $\pm$ 6.5***
80	6.7 $\pm$ 1.6	16.0 $\pm$ 3.6*	17.0 $\pm$ 3.5	18.5 $\pm$ 4.3**	20.1 $\pm$ 2.4**	29.3 $\pm$ 6.5***
100	7.0 $\pm$ 2.8	18.8 $\pm$ 4.4*	15.3 $\pm$ 5.2	19.0 $\pm$ 5.2	19.5 $\pm$ 2.2**	28.8 $\pm$ 6.1***
120	7.9 $\pm$ 3.2	17.7 $\pm$ 3.7*	17.7 $\pm$ 3.8	17.7 $\pm$ 4.7*	20.2 $\pm$ 2.5**	28.9 $\pm$ 6.7***
140	9.8 $\pm$ 2.2	14.6 $\pm$ 3.2*	15.6 $\pm$ 3.5	14.0 $\pm$ 4.4*	18.9 $\pm$ 2.3**	28.6 $\pm$ 6.7***
160	9.5 $\pm$ 1.6	13.6 $\pm$ 3.6	14.6 $\pm$ 3.5	13.7 $\pm$ 4.0	16.8 $\pm$ 2.4**	27.2 $\pm$ 6.4***
180	11.4 $\pm$ 1.8	15.8 $\pm$ 3.4	16.8 $\pm$ 3.3	13.6 $\pm$ 4.4	16.4 $\pm$ 2.7	25.0 $\pm$ 6.7***

paired *t*-test comparisons with placebo: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Duration of action

The duration of action of reproterol was measured using hourly measurements of peak flow for 9 h after dosing. Measurements were stopped once baseline values were reached so that further doses of bronchodilator could be taken. The results are shown in Figure 2 and Table 2. The mean peak flow remained above placebo levels for 3–5 h after reproterol doses between 500 μ g and 2 mg. Reproterol 4 mg and 8 mg doses both resulted in a significant improvement over baseline for all 9 h. The effective duration of action was calculated by subtracting the result following placebo from the observed result following 1 mg and 8 mg doses of reproterol for each individual. The time taken for the peak flow to fall below 75% of its peak effective value ranged from 55 to 240 min following the 8 mg dose, with a mean of 123 min ($\pm$ 33 s.e. mean). The result following the 1 mg dose was 35–240 min, mean 130 ($\pm$ 24 s.e. mean).

Figure 2 The peak flow response to inhaled reproterol, expressed as % change from baseline values.

Pulse and blood pressure measurements

There were no significant changes in pulse or blood pressure within 3 h of dosing, after any dose of reproterol. No subject complained of hand tremor or other effects apart from the taste of the inhalers, which was noted by all patients.

Discussion

Dose-response studies of a drug in the type of patient in which it is to be used are fundamental to good prescribing. This study presents the first dose-response data for reproterol administered to asthmatics from pressurised inhalers. There are many problems in performing such studies, particularly related to selection of subjects and the interpretation of the measurements of response. Subjects with 'stable' asthma are generally either in complete remission or severely obstructed, and both groups usually have trivial responses to inhaled bronchodilators. Most asthmatics who obtain benefit from bronchodilator aerosols have unstable asthma, necessitating frequent doses of bronchodilators. This study attempted to include asthmatics in this latter category. The problem with studying unstable asthmatics is the variable baseline values of lung function between different study days. Baseline values of lung function are a major determinant of response, and some method for its control must be found. We chose to control the starting baseline so that all starting values were within 10% for each individual. This frequently meant repeating study days whose baseline values fell outside the 10% variability. Since the study was truly double blind bias should not have been

Table 2 Percentage PEFR increase ($\pm$ s.e. mean) compared with six doses of reproterol over a 9 h period.

Time (h)	Dose of reproterol (mg)					
	0	0.5	1	2	4	8
1	5.9 $\pm$ 2.4	13.5 $\pm$ 3.8	13.8 $\pm$ 3.8	17.4 $\pm$ 4.3	22.5 $\pm$ 4.1	29.1 $\pm$ 5.1
2	8.4 $\pm$ 2.3	14.7 $\pm$ 2.7	14.9 $\pm$ 3.4	16.0 $\pm$ 3.5	20.6 $\pm$ 3.6	26.6 $\pm$ 5.5
3	8.7 $\pm$ 2.4	13.5 $\pm$ 3.1	15.1 $\pm$ 2.7	12.0 $\pm$ 3.2	19.0 $\pm$ 2.7	25.2 $\pm$ 5.2
4	9.4 $\pm$ 4.0	5.2 $\pm$ 3.3	12.5 $\pm$ 3.6	8.1 $\pm$ 2.1	14.1 $\pm$ 2.3	20.4 $\pm$ 2.9
5	8.1 $\pm$ 3.7	5.9 $\pm$ 3.1	9.0 $\pm$ 4.5	7.2 $\pm$ 2.4	11.3 $\pm$ 2.2	17.7 $\pm$ 3.0
6	5.8 $\pm$ 4.0	2.4 $\pm$ 2.5	7.4 $\pm$ 3.4	4.9 $\pm$ 3.0	8.1 $\pm$ 6.1	18.3 $\pm$ 3.4
7	3.5 $\pm$ 4.0	2.0 $\pm$ 1.9	4.6 $\pm$ 2.8	4.5 $\pm$ 2.7	6.7 $\pm$ 5.4	13.2 $\pm$ 3.4
8	0.7 $\pm$ 2.7	-2.4 $\pm$ 2.8	2.0 $\pm$ 2.0	4.0 $\pm$ 3.7	8.3 $\pm$ 5.8	8.2 $\pm$ 2.9
9	-1.3 $\pm$ 2.8	-3.7 $\pm$ 5.6	-3.8 $\pm$ 1.7	-0.1 $\pm$ 5.3	3.8 $\pm$ 4.1	4.1 $\pm$ 3.4

introduced by repeated study days which were found to have deviant baseline values.

Bronchodilator trials are usually carried out in the morning, at a time when baseline values of lung function are low due to the diurnal variations in these values. The FEV₁ and peak flow usually are at their best 6–8 h after waking (Hetzel & Clark, 1980). The spontaneous improvement in these values is therefore superimposed on the effect of the drug. In the present study part of the diurnal variation in peak flow is well shown by the response following placebo inhalation. This is unlikely to represent a placebo response, as its timing is completely different from the response to active drug. The true duration of response to the active drug can be calculated by subtracting the values following placebo from the values following active drug. β_2 -adrenoceptor drugs, by aerosols, such as salbutamol and terbutaline, are usually prescribed on a three or four times a day basis as studies investigating their duration of action still show significant improvement for 4–6 h (Freedman, 1972; Simonsson *et al.*, 1972). The significance is usually in terms of statistics rather than of clinical benefit. A patient with a good bronchodilator response wants to maintain that response near its maximum. To try and obtain an estimate of the effective duration of action the time taken to fall below 75% of the maximum achieved has been calculated. This time is 130 min following the standard 1 mg dose and 123 min following an 8 mg dose. This time is the repetition time from the point of view of the patient. However, if a second dose is taken when there is still a 75% response to the first dose, the baseline will be higher and the dose response characteristics may be very different. Studies with salbutamol and terbutaline have also shown

a relatively brief plateau at the top of the response-duration curves, with improvement falling below 75% of maximum at 2–3 h (Freedman, 1972; Simonsson *et al.*, 1972).

There is a considerable need for a long acting β_2 -adrenoceptor agonist given by inhalation. At present the only method of prolonging the duration of action is by increasing the dose. Although with all doses up to 8 mg the real effect is below 75% of peak by 130 min. The present study clearly shows the effects of prolonging the duration of action by increasing the dose. The 8 mg dose was shown to be effective, and no adverse effects were observed. The study also suggests that the response to reproterol may be bimodal, with a first plateau of response achieved with the 1 mg dose, with a second increase in dose achievable with an 8 mg dose. It is possible that a non-linear dose-response accounts for the improvement seen with nebulised adrenoceptor bronchodilators over and above that seen when the same drug is given by a pressurised inhaler in a dose at which the initial dose-response curve has flattened. The only study of the response to nebulised reproterol compared the 30 min response to 2.5 and 5 mg dose, with equivalent responses to each (Voss & Aurich, 1979). In that study, neither the dose ranges nor the duration of measurement were sufficient to investigate this hypothesis.

The present study shows that improvement in the peak effect and duration of action of inhaled reproterol can be achieved by increasing the dose to 8 mg, without producing changes in pulse rate or blood pressure.

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