

# Prazosin in the treatment of chronic asthma

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**ABSTRACT** The role of prazosin, an  $\alpha_1$  adrenoceptor blocker, was investigated in patients with chronic stable asthma who continued to have symptoms despite conventional treatment. Forty patients were entered into a double blind, placebo controlled, crossover trial to examine the effect of adding oral prazosin (2 mg twice daily) to previous medication for three weeks. Sixteen patients withdrew from the study. The remaining 24 patients showed no significant change in peak expiratory flow, FEV<sub>1</sub>, forced vital capacity (FVC), FEV<sub>1</sub>/FVC ratio, diary card symptom scores, or dose of  $\beta$  sympathomimetic.

Several studies have suggested that  $\alpha$  adrenoceptor function may be altered in asthma.<sup>1-3</sup> As a result there has been speculation on the role of  $\alpha$  adrenoceptor antagonists in the treatment of asthma. Most studies have examined the acute bronchodilating effect of  $\alpha$  adrenoceptor antagonists, with conflicting results,<sup>4-12</sup> and the range of pharmacological properties these drugs possess has made interpretation difficult.<sup>7</sup> Alpha receptors in the lung also mediate mast cell release<sup>13</sup> and mucus secretion<sup>14</sup> and longer term treatment with  $\alpha$  adrenoceptor antagonists might improve airflow obstruction by mechanisms other than direct smooth muscle relaxation. Few studies, however, have looked at the effect of a longer period of treatment with  $\alpha$  blockers. We have studied the effects of prazosin, a selective  $\alpha_1$  adrenoceptor blocker,<sup>15</sup> given for three weeks to patients with chronic asthma who despite conventional anti-asthma treatment continued to have symptoms.

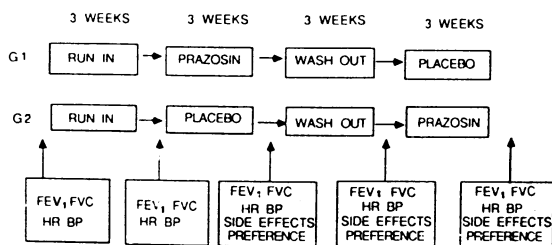
## Methods

### PATIENTS

We studied 40 patients aged 18-69 years with chronic asthma who continued to have symptoms despite conventional anti-asthma treatment. All subjects were taking a  $\beta$  sympathomimetic drug, 38 inhaled and 15 oral steroids, two ipratropium bromide, and 19 xanthines. All had had documented variability in peak flow (PEF) or FEV<sub>1</sub>, either spontaneously or after bronchodilator, of 20% or more during the previous year. Patients gave written, informed consent to the study, which had been approved by the local research and

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*Design of the trial, with the information collected at clinic visits shown in the bottom row of boxes. FEV<sub>1</sub>—one second forced expiratory volume; FVC—forced vital capacity; HR—heart rate; BP—blood pressure. "Preference" refers to treatment in the prazosin, placebo, and washout periods.*

ethics committee. All patients were maintained on their previous medication in constant dosage and were withdrawn if this was changed.

### TRIAL DESIGN

The study had a randomised, double blind, placebo controlled crossover design<sup>16</sup> with a pretreatment stabilisation period and two treatment periods separated by a washout period (figure). Each period was three weeks. Prazosin and placebo were supplied as identical capsules. The stepwise increases in prazosin dosage were: 0.5 mg prazosin the first evening and then 0.5 mg twice daily for four days, 1 mg twice daily for four days, and 2 mg twice daily for 13 days.

### MEASUREMENTS

At each visit peak expiratory flow (PEF), one second forced expiratory volume (FEV<sub>1</sub>), and forced vital capacity (FVC) and also blood pressure and heart rate were recorded, and the remaining capsules were

counted. Patients were asked whether they preferred the current or a previous treatment.

A diary card was completed each morning and evening to record: (1) Morning: number of times woken in the night, and did asthma wake the patient early? (yes/no); how was the asthma last night? (scale 1-4: 1 for no symptoms, 4 for severe symptoms); number of puffs of bronchodilator during the night; PEF (best of three attempts) before bronchodilator and 20 minutes afterwards. (2) Evening: number of puffs of bronchodilator used since morning; how was the asthma during the day? (scale 1-4 as above); PEF (as above).

#### STATISTICAL ANALYSIS

The two treatment order groups were analysed separately to exclude any order effect of treatment. None was found and so combined data are presented. Data were analysed according to the method of Hills and Armitage<sup>16</sup> for a two treatment, two period crossover design and significance levels were assessed by Student's *t* test. Data for asthma severity and early morning waking were not normally distributed, so a non-parametric (Wilcoxon) test was used for analysis of these results. Calculating the power of the study,<sup>16</sup> on the basis of the 24 patients who completed the trial, showed that there was a 90% chance of detecting a true difference in PEF of 10 l/minute.

#### Results

##### PATIENTS WITHDRAWN FROM THE STUDY

Forty patients entered the study and 24 of these completed the trial (table 1). The age and sex distribution were similar for the two treatment order groups, with a similar number of withdrawals from each group. Sixteen patients withdrew during the study. Their baseline lung function was similar to that of the patients completing the study (table 1). Seven withdrawals were not relevant to the trial outcome (four during the run in period due to non-attendance (2) and treatment changes (2), one due to unsatisfactory home

Table 1 Age, sex, and initial lung function in patients who completed the study and in those who withdrew (mean (SEM) unless otherwise stated)

|                               | Completed   | Withdrew    |
|-------------------------------|-------------|-------------|
| Number                        | 24          | 16          |
| Mean (SD) age (y)             | 47 (14)     | 53 (13)     |
| Sex (M/F)                     | 9/15        | 10/6        |
| Morning peak flow (l/min):    |             |             |
| Before bronchodilator         | 233 (28)    | 195 (20)    |
| After bronchodilator          | 283 (29)    | 252 (18)    |
| FEV <sub>1</sub> (l)          | 1.5 (0.1)   | 1.4 (0.2)   |
| [predicted FEV <sub>1</sub> ] | [2.7 (0.2)] | [2.7 (0.2)] |
| Forced vital capacity         | 2.5 (0.2)   | 2.7 (0.3)   |
| [predicted FVC]               | [3.5 (0.2)] | [3.8 (0.3)] |

Table 2 Mean (SEM) peak flow before and after bronchodilator, FEV<sub>1</sub>, forced vital capacity (FVC), and FEV<sub>1</sub>/FVC ratio and asthma severity scores for patients taking prazosin and placebo\*

|                                  | Placebo   | Prazosin  |
|----------------------------------|-----------|-----------|
| Peak flow (l/min):               |           |           |
| Morning:                         |           |           |
| Before                           | 245 (29)  | 238 (30)  |
| After                            | 291 (31)  | 289 (31)  |
| Evening:                         |           |           |
| Before                           | 272 (28)  | 262 (31)  |
| After                            | 307 (30)  | 306 (31)  |
| FEV <sub>1</sub> (l)             | 1.5 (0.1) | 1.6 (0.1) |
| FVC (l)                          | 2.5 (0.2) | 2.6 (0.2) |
| FEV <sub>1</sub> /FVC (%)        | 63 (5)    | 62 (4)    |
| Severity score†                  |           |           |
| Day                              | 2.0 (0.2) | 2.0 (0.2) |
| Night                            | 1.8 (0.2) | 1.9 (0.2) |
| No of times woken                | 1.0 (0.3) | 1.0 (0.3) |
| No of aerosol puffs during day   | 7.0 (1.1) | 7.0 (0.9) |
| No of aerosol puffs during night | 0.9 (0.4) | 0.9 (0.3) |

\*None of the differences is statistically significant.

†See under "Measurements."

recordings, and two due to other diseases). Four patients withdrew because of worsening asthma, two while taking placebo, one while taking prazosin, and one during the washout period. The other five withdrawals were due to side effects—two during the placebo period and three during prazosin treatment. They included headache (2), blurred vision (1), dizziness (1), and nausea (1).

##### PATIENTS COMPLETING THE STUDY

##### Lung function, severity scores, and preference

There was no significant difference between the placebo and the prazosin periods in any measure of asthma severity, nor were there significant differences in mean PEF during the last seven days of each treatment period, FEV<sub>1</sub>, FVC, or FEV<sub>1</sub>/FVC ratio (table 2). Most patients were woken every night by their asthma and described their daytime symptoms as moderate. Seventeen patients expressed a preference for one of the treatment periods, two preferring the prazosin, seven the placebo, and eight the washout period.

##### Side effects

Twenty eight patients reported side effects (mostly dizziness, headache, and malaise)—12 of the 16 who withdrew and 16 of the 24 who completed the study. Patients who completed the study reported 13 episodes while taking prazosin and five while taking the placebo—but no particular side effect occurred more commonly with either treatment. There was no significant difference in mean (SEM) heart rate (placebo 82 (4), prazosin 81 (4)) or blood pressure (systolic: placebo 141 (6), prazosin 141 (6); diastolic: placebo 84 (4), prazosin 82 (5)).

## Discussion

Previous studies on the role of  $\alpha$  adrenoceptor antagonists in the treatment of asthma have produced variable results.<sup>4-6,8-10</sup> Selection of patients, the type and time course of the study, and other pharmacological actions of the drug used may have contributed to these different findings. Studies of the acute effect of  $\alpha$  receptor blockade in patients with stable asthma have shown little or no response to the drug alone but some potentiation with  $\beta$  sympathomimetics. Britton *et al*<sup>6</sup> gave a single dose of thymoxamine to 10 asthmatic patients who had stopped medication for the day of the study and found no improvement in lung function. Gaddie *et al*<sup>5</sup> found that intravenous indoramin alone produced no bronchodilation but potentiated the effect of salbutamol. Alpha adrenoceptor antagonists may be effective in exercise, cold, and histamine induced asthma.<sup>8-12</sup> Bianco *et al*<sup>8</sup> studied 11 patients with exercise induced asthma and found that indoramin prevented the fall in specific airways conductance.

Possible longer term effects of  $\alpha$  receptor blockade on asthma have been little studied. Campbell *et al*<sup>4</sup> treated 32 patients with indoramin for four weeks and found a small increase in PEF with treatment. Only 13 of their patients showed an initial reversibility of 20% in FEV<sub>1</sub> and only two of these showed a significant improvement with treatment. We have examined the possible value of an  $\alpha$  adrenoceptor antagonist as additional treatment in a group of patients with moderately severe chronic asthma over a period that should be sufficient for the appearance of any longer term improvement in lung function due to alterations in mucus secretion or mast cell "stabilisation." By using a specific  $\alpha$  adrenoceptor blocker, prazosin, we have excluded the other therapeutic effects that most of the agents used in previous trials possess.<sup>7,17</sup>

Using both objective and subjective measures of asthma severity, we have found no additional therapeutic benefit from prazosin. Our findings support the work of Barnes *et al*,<sup>7</sup> who found no bronchodilator effect of nebulised prazosin given as a single dose to adults with asthma. Marlin *et al*<sup>18</sup> reported bronchodilatation accompanying mild hypotension after a 1 mg oral dose of prazosin. With a higher daily dose used for three weeks we have not observed additional bronchodilatation. No circulatory effects were noted, although more symptoms were reported in the treatment group. Prazosin is likely to be safe for treating hypertension in asthmatic patients. Alpha adrenoceptor antagonists may have some role in the treatment of exercise induced asthma, but we have found no evidence for any additional therapeutic benefit from this dose of prazosin when

given for three weeks to a group of patients with chronic asthma maintained on conventional anti-asthma treatment.

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