

# Inhaled prazosin in asthma

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**ABSTRACT** Prazosin, a potent and selective alpha-adrenergic antagonist, was given by inhalation to nine asthmatic subjects aged 25-48 years (six with positive skin tests). Prazosin 0.5 mg, salbutamol 1 mg, or placebo were given by nebuliser in randomised double-blind fashion on separate days. Although all subjects showed a significant increase in FEV<sub>1</sub>, vital capacity, and maximum expiratory flow at 70% of total lung capacity after salbutamol, there was no significant difference between prazosin and placebo. This suggests that alpha-adrenergic receptors are not important in the control of bronchial tone in asthma. The weak bronchodilatation ascribed to alpha-antagonists in previous studies could be explained by other pharmacological actions of the drugs used.

Alpha-adrenergic receptors which mediate bronchoconstriction have been demonstrated in isolated airway preparations of several mammalian species including man,<sup>1-5</sup> but their significance in the pathogenesis of asthma is uncertain. In the presence of beta-adrenergic blockade, alpha-adrenergic agonists, such as phenylephrine and methoxamine, cause a moderate degree of bronchoconstriction in asthmatic, but not in normal subjects.<sup>4-6-8</sup> Conversely alpha-adrenergic antagonists such as phenoxybenzamine, phentolamine, and thymoxamine may prevent bronchospasm induced by histamine,<sup>9-11</sup> exercise,<sup>12-13</sup> or allergen challenge,<sup>14</sup> and increase airways conductance in asthmatics.<sup>14-15</sup> However, interpretation is often difficult as the alpha-blocking drugs previously used have other actions such as antihistamine activity, and when given systemically tend to cause hypotension which may result in reflex sympathetic activation and bronchodilatation.

Prazosin is the most potent and specific adrenergic antagonist available and has no antihistamine activity.<sup>16-17</sup> We have therefore measured its effect on airways function in asthmatic subjects in order to investigate the role of alpha-adrenoceptors in asthma. Prazosin was given by inhalation to avoid changes in blood pressure which might activate a sympathetic reflex.

## Methods

Nine stable asthmatics attending the chest clinic at Hammersmith Hospital, who had a bronchodilator response to inhaled salbutamol (greater than 20% increase in FEV<sub>1</sub>) were studied (table). Research Ethics Committee approval for the study was obtained and all subjects gave informed consent. All bronchodilator therapy was stopped at least 12 hours before study and measurements were started at about 0900 h. Forced expiratory volume in one second (FEV<sub>1</sub>), vital capacity (VC), and maximum expiratory flow at 70% of total lung capacity (Vmax<sub>70</sub>) were measured by Krogh spirometer. The best of three consecutive measurements, corrected to BTPS, was taken. Blood pressure (BP) lying and standing was recorded by Arteriosonde (Roche) and heart rate by palpation of the radial pulse. Symptoms were recorded before each measurement.

After baseline readings subjects inhaled from a Wright nebuliser driven by compressed air at 10 litres/min during tidal breathing until 2 ml had been nebulised (10-12 min). Either prazosin 0.5 mg, salbutamol 1.0 mg, or placebo (lactate and dextrose vehicle, pH 4.5) was given in a random double-blind manner on separate days. Baseline measurements each day were within 15% of each other and tests were postponed when values were outside this range. FEV<sub>1</sub>, Vmax<sub>70</sub>, lying and standing BP, and heart rate were recorded immediately,

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Table Anthropometric and baseline pulmonary function measurements in the nine asthmatic subjects studied

Subject	Sex	Age (yr)	Height (cm)	Weight (kg)	Skin tests	FEV <sub>1</sub>		VC	
						Actual	Predicted	Actual	Predicted
1	M	48	169	76.5	+	1.35	2.98	3.90	3.99
2	M	28	155	67.0	+	0.97	3.36	2.73	3.82
3	M	36	173	70.5	+	3.03	3.80	4.80	4.62
4	M	48	165	78.0	+	0.60	3.17	2.95	3.74
5	M	25	175	63.5	-	1.05	4.19	2.75	5.09
6	M	31	179	60.0	+	0.73	4.17	1.95	5.16
7	F	29	161	62.0	+	1.26	2.78	2.84	3.49
8	F	33	165	50.0	-	2.00	2.35	3.36	2.95
9	F	38	153	43.5	-	1.36	2.40	2.46	2.92
Mean		35.1		63.4		1.37	3.24	3.08	2.98

then 5, 10, 15, 30, 45, and 60 minutes after inhalation.

Results were analysed by Student's *t* test.

**Results**

There was no significant difference ( $p > 0.1$ ) in baseline FEV<sub>1</sub> before inhalation of placebo, prazosin, or salbutamol ( $1.37 \pm 0.74$  l,  $1.38 \pm 0.66$  l, and  $1.43 \pm 0.70$  l respectively; mean  $\pm$  SEM,  $n = 9$ ). Inhalation did not cause bronchial irritation or other symptoms in any of the subjects. There were no significant changes in FEV<sub>1</sub> (fig 1) after inhala-

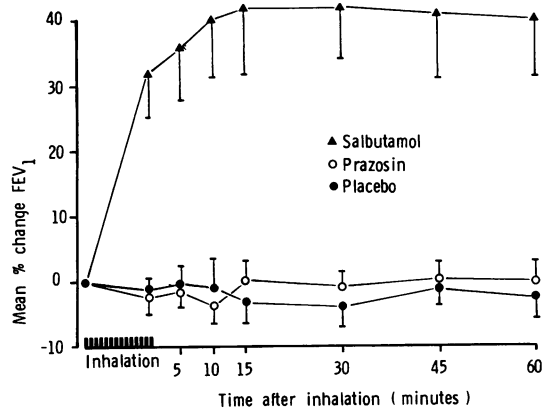


Fig 1 Mean ( $\pm$ SEM) percentage change in FEV<sub>1</sub> after inhalation of prazosin 0.5 mg (○), salbutamol 1 mg (▲), or placebo (●) in nine asthmatic subjects.

tion of placebo or prazosin, although there was a marked response to salbutamol (FEV<sub>1</sub>  $2.16 \pm 0.78$  l 15 min after inhalation). No significant change in VC occurred with placebo or prazosin but a significant increase occurred with salbutamol.

There was no change in Vmax<sub>70</sub> after inhalation of either placebo or prazosin but a very significant ( $p > 0.001$ ) increase after salbutamol ( $0.22 \pm 0.10$

to  $0.72 \pm 0.25$  l s<sup>-1</sup>) (fig 2). There were no significant changes in heart rate or BP after prazosin or salbutamol.

The prazosin solution used for inhalation had the expected pharmacological activity when assayed by inhibition of specific <sup>3</sup>H-prazosin binding to alpha-adrenergic receptors in a guinea pig lung homogenate as described previously.<sup>18</sup>

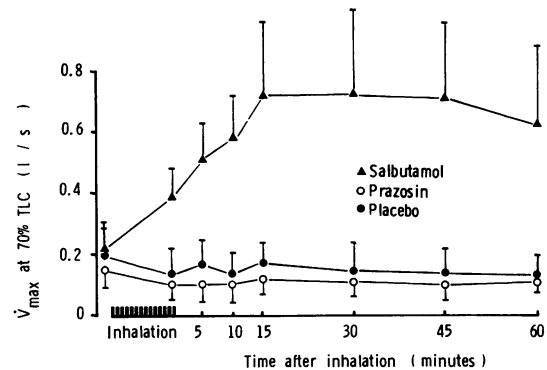


Fig 2 Mean ( $\pm$ SEM) change in maximum expiratory flow at 70% of total lung capacity after inhalation of prazosin 0.5 mg (○), salbutamol 1 mg (▲), or placebo (●) in five asthmatic subjects.

**Discussion**

Szentivanyi<sup>19</sup> proposed that in asthma there is a reduced responsiveness of beta-adrenergic receptors with a compensatory increased responsiveness of alpha-receptors. The beta-hyporesponsiveness demonstrated in asthmatics, however, appears to be caused mainly by the effects of treatment with beta-agonist bronchodilators. The role of alpha-adrenoceptors in asthma remains controversial. Although no alpha-adrenergic mediated bronchoconstriction could be demonstrated in bronchial smooth muscle taken at necropsy from

patients with normal lungs, airways from patients with chronic obstructive airways disease showed alpha-agonist mediated bronchoconstriction, suggesting that alpha-receptors are in some way activated by airways disease. This is confirmed in vivo by the finding that alpha-agonists in the presence of beta-blockade cause bronchoconstriction in asthmatics but not in normal subjects.<sup>4-8</sup> There is some evidence for a generalised alpha-adrenergic hyper-responsiveness in asthmatics with increased cutaneous vasoconstriction and pupillary dilatation of alpha agonists.<sup>20</sup> Recently using radioligand binding techniques, it has been possible to show a slight reduction in pulmonary beta receptor number but a marked increase in alpha receptor number in experimental asthma in guinea pigs.<sup>21</sup>

These studies suggest that alpha-blockade should produce bronchodilatation in asthmatics and several studies have shown that alpha-antagonists may prevent histamine, allergen, and exercise-induced bronchospasm and increase airways conductance.<sup>9-15</sup> However, the alpha-antagonists used in these studies have all had other pharmacological actions which could account for the bronchodilator or inhibitory effects demonstrated. Phenoxybenzamine and thymoxamine have significant anti-histamine effects,<sup>22</sup> phentolamine has a direct inhibitory effect on smooth muscle,<sup>23</sup> and all cause block of the presynaptic alpha-adrenoceptor which would have the effect of increasing the amount of noradrenaline released by sympathetic nerves.<sup>24</sup> Prazosin, however, is a potent and specific alpha-antagonist which is selective for the postsynaptic alpha-receptor and it has no antihistamine activity. When given by inhalation it caused no change in blood pressure or pulse indicating that there was no baroreflex stimulation of the sympathetic nervous system and increase in circulating noradrenaline which occurs when alpha-blockers are given systemically leading to a fall in blood pressure.

Prazosin, when given by inhalation, appeared to have no significant bronchodilator effect in asthmatics who all showed a marked response to salbutamol. There are several possible reasons why prazosin may have been ineffective in this study. Firstly, the dose chosen may have been inadequate to cause significant alpha-adrenergic blockade in the lung. This dose was one-tenth of that known to cause substantial alpha-blockade when given orally (5 mg).<sup>25</sup> In comparison 0.1 mg of salbutamol given by inhalation produces a similar degree of bronchodilatation to 2 mg taken orally, giving a ratio of inhaled to oral dose of 1:20.<sup>26</sup> It is possible that penetration of prazosin into the

epithelium of the airway was slow and incomplete. This is unlikely as the oil:water partition coefficient of prazosin at pH 7.4 is approximately 100 and it is well absorbed orally, suggesting good mucosal penetration. That the prazosin solution inhaled may have lost activity is unlikely as pharmacological potency was maintained when assayed by a radioligand binding method. The method of nebulisation was adequate as salbutamol delivered in the same way provoked significant bronchodilatation.

The lack of effect of prazosin in this study suggests that alpha-adrenergic receptors are unimportant in the control of bronchial tone in asthmatics. Alpha receptor stimulation of passively sensitised human lung causes increased release of bronchoconstrictor mediators such as histamine and slow reacting substance of anaphylaxis.<sup>27</sup> It is possible that alpha-antagonists may prevent exercise and antigen-induced asthma by inhibiting the release of mediators rather than by a direct effect on bronchial smooth muscle. Studies are in progress to investigate this hypothesis. It has recently been shown that alpha-adrenergic receptors mediate secretion from tracheal submucous glands in the cat.<sup>28</sup> Although there is no direct evidence in man, it is possible that alpha-antagonists may reduce bronchial mucus secretion which could reduce the mucus plugging that occurs in severe asthma.

This work was supported by Medical Research Council Programme Grant G 971/16/C. We are very grateful to Pfizer, Sandwich, Kent for supplying the prazosin and for their helpful advice.

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