BRONCHODILATOR ACTIVITY OF PRAZOSIN IN PATIENTS WITH ALLERGIC RHINITIS AND ASTHMA

The effect on pulmonary function of the α_1-adrenoceptor antagonist, prazosin, was determined in two double-blind studies. In the first study, prazosin (1 mg) was compared with metoprolol (100 mg), propranolol (80 mg) and placebo given orally in a balanced, randomized design in eight subjects (six males, two females, aged 22 to 37 years) with a past history of either mild asthma or allergic rhinitis. No subject had symptoms of asthma during the preceding 6 months and their forced expiratory volume in one second (FEV_1) was within 15% of predicted normal. Atopic status was assessed and seven subjects demonstrated two or more positive skin prick reactions to common allergens. An histamine provocation test was performed and seven subjects demonstrated bronchial hyperreactivity with the histamine concentration causing a 20% fall in FEV_1 ranging from 0.03 to 8.0 mg/ml (abnormal $\leq$ 8.0 mg/ml). Informed, written consent was obtained. The trial was conducted in the morning of four days at weekly intervals. Placebo tablets were prepared with the same appearance and taste to all active drugs. Pulmonary function was assessed by expiratory flow rate at 50% vital capacity ($\dot{V}_{50}$) measured from a forced expiratory flow volume curve (volume-displacement plethysmograph) and FEV_1 (Godart Expirograph). Three forced expiratory flow-volume curves and FEV_1 measurements (1 min intervals) were taken before and two readings of each test at 0.5, 1, 1.5, 2, 3, 4 and 6 h after each treatment with the best value on each occasion used for comparisons. Before the pulmonary function tests, blood pressure and pulse rate were recorded in the supine position after a 10 min rest. Venous blood samples were taken at these times for prazosin estimation (Twomey & Hobbs, 1978). The subjects had a light breakfast 1 h before the study and lunch was taken after 4 h. The results were submitted to an analysis of variance followed by the Duncan's Multiple Range Test. It was also considered that differences between treatments should equal or exceed double the coefficient of variation for basal values to be significant.

In the second study, eight patients (six males, two females, aged 20 to 74 years) were selected and informed, written consent was obtained. Four patients had asthma and four chronic bronchitis with asthma. Their FEV_1 ranged from 25 to 75% of predicted normal. They were stabilized on maintenance therapy with no recent exacerbations of asthma (salbutamol aerosol −8, beclomethasone diproprionate −5, prednisone −4, oral theophylline −5) and it was necessary for there to be less than 20% variation between basal FEV_1 values. Five patients had an elevated systolic (142–208 mm Hg) and four an elevated diastolic blood pressure (96–120 mm Hg), although none had received anti-hypertensive treatment. The study was a randomized, crossover design, performed in the morning of two days separated from each other by at least 48 h. The two treatments were 1 mg oral prazosin and placebo. Inhaled salbutamol (12 h) and oral theophylline (72 h) were withdrawn before each study day, but oral and inhaled corticosteroids were continued at maintenance doses. Three FEV_1 readings (1 min intervals) were performed before and two at 0.5, 1, 2, 3, 4 and 6 h after each treatment and the best reading on each occasion was used for comparisons. Blood pressure, pulse rate and venous blood samples for prazosin estimation were taken as in the first study with the same meal arrangements. Immediately after the 6 h FEV_1 recording, 200 μg salbutamol by pressurized aerosol was given and two FEV_1 readings were repeated after 30 min. The results were analyzed using the paired Student's *t*-test.

In the first study, the mean % $\dot{V}_{50}$ changes from control are shown in Figure 1. The mean % FEV_1 changes from control, the mean pulse rate, systolic and diastolic blood pressure changes from control, and the mean (s.e. mean) plasma prazosin levels are shown in Table 1. The mean coefficient of variation

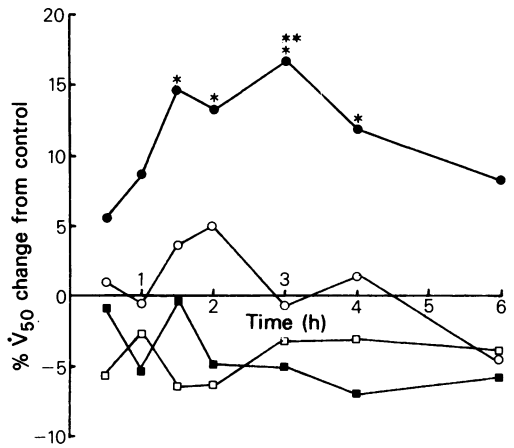

Figure 1 The mean % $\dot{V}_{50}$ changes from control after 1 mg prazosin ●, 100 mg metoprolol ■, 80 mg propranolol □ and placebo ○ for the eight subjects. Mean (s.e. mean) basal $\dot{V}_{50}$ values were 3.8 (0.3) for prazosin, 4.0 (0.3) for metoprolol, 4.0 (0.3) for propranolol and 4.0 (0.3) l/s for placebo.
Significance values: prazosin > metoprolol, propranolol ($P < 0.05$)*, prazosin > placebo ($P < 0.05$)**

Table 1 The mean % FEV_1 change from control and the mean pulse rate, systolic and diastolic blood pressure changes from control after 1 mg prazosin, 100 mg metoprolol, 80 mg propranolol and placebo and the mean (s.e. mean) plasma prazosin levels for the eight subjects.

	Time (h)						
	0.5	*1.0*	*1.5*	*2.0*	*3.0*	*4.0*	*6.0*
	Mean % FEV_1 change from control[××]						
Prazosin	0.2	2.4[+°]	2.5[+]	4.7[+°]	1.9	3.1	3.5
Metoprolol	1.2	−1.2	−2.4	−0.4	0.3	0.7	−0.6
Propranolol	−2.0	−1.6	−0.8	−1.2	0.5	2.1	−1.0
Placebo	0.1	−0.1	0.2	0.6	2.3	1.1	1.3
	Mean pulse rate change from control (beats/min)						
Prazosin	−1.6[+°]	1.6[+°]	−0.9[+°]	0.6[*+°]	−1.3[+°]	−0.6[+°]	5.0[+°]
Metoprolol	−10.8[×]	−17.4[×]	−17.6[×]	−17.5[×]	−15.6[×]	−14.8[×]	−14.4[×]
Propranolol	−10.4[×]	−14.4[×]	−18.5[×]	−16.8[×]	−15.8[×]	−11.5[×]	−11.8[×]
Placebo	−2.1	−2.5	−5.6	−6.4	−4.9	−0.5	−0.6
	Mean systolic blood pressure change from control (mm Hg)						
Prazosin	−4.1	−4.6	−7.6[×]	−7.0	−10.6	−8.3	−5.6[×]
Metoprolol	−3.4	−8.9[×]	−8.1[×]	−8.8	−8.4	−6.9	−8.6[×]
Propranolol	−3.3	−7.0[×]	−7.0[×]	−8.0	−10.6	−8.8	−7.9[×]
Placebo	1.5	2.6	1.3	0.6	−0.5	0.1	3.0
	Mean diastolic blood pressure change from control (mm Hg)						
Prazosin	0	−0.5	−4.1	−3.1	−2.8	−4.0	0°
Metoprolol	−1.1	−2.8	−3.5	−4.8	−3.9	−6.3	−4.6
Propranolol	−4.1	−4.0	−4.0	−4.6	−5.9	−7.4	−9.6[×]
Placebo	−0.8	−0.3	−2.3	2.3	−3.4	−5.3	−0.4
	Mean plasma prazosin (nmol/l)						
	12.7	16.4	20.0	15.9	14.0	13.0	10.4
	(5.2)	(3.6)	(3.1)	(2.3)	(2.1)	(0.8)	(2.3)

[+] prazosin > metoprolol ($P < 0.05$), [°] prazosin > propranolol ($P < 0.05$)
[*] prazosin > placebo ($P < 0.05$), [×] metoprolol, propranolol, prazosin < placebo ($P < 0.05$)
[××] Mean (s.e. mean) basal FEV_1 (l): 4.07 (0.34)—prazosin
4.02 (0.35)—metoprolol
4.05 (0.35)—propranolol
4.03 (0.31)—placebo

was 7.3% for $\dot{V}_{50}$ and 3.2% for FEV_1 basal values. Prazosin produced a significant $\dot{V}_{50}$ bronchodilator response greater than baseline variability compared with placebo (3 h) and the β-adrenoceptor antagonists (1.5–4 h). The FEV_1 response with prazosin was significantly greater than with the β-adrenoceptor antagonists between 1 and 2 h, but the differences did not exceed baseline variability. Metoprolol and propranolol produced equivalent significant reductions in pulse rate and there were similar significant falls in blood pressure with all drugs.

These results confirm those we found in a preliminary study of prazosin in two patients with a history of mild asthma (Marlin *et al.*, 1981). Neither pulmonary function test was sufficiently sensitive to detect a significant bronchoconstrictor response with propranolol. The doses of metoprolol and propranolol used have been shown to produce equivalent cardiac β-adrenceptor blockade (Oh *et al.*, 1978). However, no differential bronchial response was demonstrated between the non-selective propranolol and metoprolol which possesses bronchosparing properties (Kumana & Marlin, 1978). Specific protocol criteria are required when differences in cardioselectivity between β-adrenoceptor antagonists are being investigated (McDevitt, 1978) and more sensitive pulmonary function tests, e.g. partial flow volume curves, may be necessary in subjects with normal airflow resistance (Ingram & McFadden, 1977; Pride, 1979).

In the second study, the mean % FEV_1 changes from control are shown in Figure 2. The mean pulse rate, systolic and diastolic blood pressure changes from control and the mean (s.e. mean) plasma prazosin levels are shown in Table 2. The mean coefficient of variation was 11.2% for FEV_1 basal values. There were significant differences between the FEV_1 responses for prazosin and placebo at 4 and

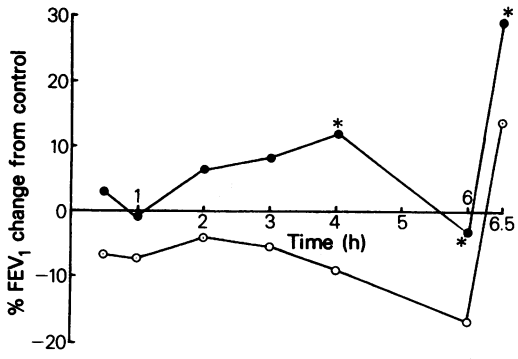

Figure 2 The mean % FEV_1 changes from control after 1 mg prazosin ● and placebo ○, and after 200 μg salbutamol by pressurized aerosol administered at 6 h for the eight asthmatic patients. Mean (s.e. mean) basal FEV_1 values were 1.28 (0.22) for prazosin and 1.46 (0.26) l for placebo.
Significance value: prazosin > placebo ($P < 0.05$)*

6 h and also after salbutamol inhalation, and these were of similar order of magnitude to baseline FEV_1 variability. The absolute mean prazosin response was small (12% FEV_1 increase from control) and could be explained by spontaneous variation in the patients pulmonary function. However, prazosin inhibited the bronchoconstrictor response observed with placebo. The decline in FEV_1 after placebo was considered to be related to withdrawal of the patients regular bronchodilator treatment. The patients had asthmatic symptoms before treatment on each study day. Inhaled salbutamol produced 33% FEV_1 improvement on each day. Comparison of the FEV_1 salbutamol and prazosin responses on the same day indicated that salbutamol was at least three times more potent with respect to the doses used. Prazosin produced a significant fall in blood pressure.

These results indicate that prazosin possesses mild bronchodilator activity in some subjects with bronchial hyperreactivity and also in some asthmatic patients with airflow obstruction. The effects of higher oral doses of prazosin require further investigation. Recently, Barnes *et al.* (1980) showed that 0.5 mg prazosin by inhalation produced no bronchodilator effect in asthmatic patients, but no information was given regarding the stability and physical properties of the prazosin solution used for nebulization. The bronchodilator activity of prazosin observed in these studies may be due to direct antagonism of α-adrenoceptors in bronchial smooth muscle. α-adrenoceptors are present in human lung (Barnes *et al.*, 1980b) and there may be increased numbers in experimental asthma (Barnes *et al.*, 1980a). Bronchodilator activity in human asthma has been reported with other α-adrenoceptor antagonists, but this may be related to other pharmacological actions of these drugs, e.g. antihistaminic activity, effects on release and uptake of catecholamines (Patel, 1976). Antagonism of mast cell α-adrenoceptors will inhibit bronchoconstrictor mediator release, but this may only be relevant in the presence of antigenic challenge to sensitized mast cells (Orange *et al.*, 1971). Prazosin is also a phosphodiesterase inhibitor with greater potency than theophylline, but its vasodilator activity occurs at concentrations less than those required for phosphodiesterase inhibition (Hess, 1974; Wood *et al.*, 1976; Cambridge *et al.*, 1977). Hypotension produced by α-adrenoceptor antagonists causes baroreflex sympathetic stimulation which could lead to mild bronchodilatation, but this is unlikely with prazosin

Table 2 The mean pulse rate, systolic and diastolic blood pressure changes from control after 1 mg prazosin and placebo and the mean (s.e. mean) plasma prazosin levels for the eight asthmatic patients.

	Time (h)					
	0.5	*1.0*	*2.0*	*3.0*	*4.0*	*6.0*
	Mean pulse rate change from control (beats/min)					
Prazosin	−1.5	0.5	−1.3	−2.8	1.8	−1.3
Placebo	−3.8	−5.8	−6.0	−6.0	−2.3	−0.5
	Mean systolic blood pressure change from control (mm Hg)					
Prazosin	−13.8	−29.0	−23.3×	−18.0	−18.5	−15.9
Placebo	−4.0	−7.0	−4.8	−5.0	0.8	0.3
	Mean diastolic blood pressure change from control (mm Hg)					
Prazosin	−9.5	−11.5×	−11.3×	−7.3	−10.0	−7.5
Placebo	−2.3	−0.8	−0.3	−0.8	1.3	1.3
	Mean plasma prazosin level (nmol/l)					
	13.0	17.2	17.7	19.0	16.9	10.7
	(6.2)	(6.2)	(3.1)	(2.1)	(1.3)	(2.3)

× prazosin < placebo ($P < 0.05$)

which does not evoke the expected baroreceptor-mediated compensatory rise in cardiac output and heart rate (Stokes & Oates, 1978).

All β-adrenoceptor antagonists, including those with relative cardioselectivity compared with propranolol, have the potential to precipitate airflow obstruction in patients with asthma and chronic obstructive bronchitis (Kumana & Marlin, 1978). An anti-hypertensive drug which possesses bronchodilator activity would provide an important therapeutic advantage for the management of hypertension in patients with airflow obstruction. This work provides pharmacodynamic support for the use of prazosin as anti-hypertensive treatment in patients with asthma or chronic obstructive bronchitis.

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INTERACTION BETWEEN FLURBIPROFEN AND INDOMETHACIN IN RHEUMATOID ARTHRITIS

Many non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to interact with aspirin with changes in serum drug levels and alterations in clinical effects (Brooks *et al.*, 1975; Rubin *et al.*, 1973; Segre *et al.*, 1974). These studies are particularly relevant because of the possibility of self-administration of aspirin by patients already receiving such drugs. However, as the number and availability of NSAIDs increases the potential for their interaction becomes considerable (Miller, 1981).

Flurbiprofen and indomethacin are both widely used anti-inflammatory drugs and known pharmacokinetic interactions occur between each drug and aspirin (Brooks & Khong, 1977; Kwan *et al.*, 1978).