α -ADRENOCEPTOR BLOCKING DRUGS IN ASTHMA

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- 1 The effect of α -adrenoceptor blocking drug, thymoxamine alone and in combination with isoprenaline, was studied on the specific airways conductance (SGaw) in ten patients with extrinsic asthma.
- 2 Thymoxamine when given together with isoprenaline produced significantly greater increase in SGaw as compared to improvement achieved with isoprenaline alone.
- 3 It is suggested that the potentiation of isoprenaline induced bronchodilatation by thymoxamine is mediated by increased cyclic AMP formation in the bronchial smooth muscle.

Introduction

α -adrenoceptors are present in mammalian lungs and pharmacological stimulation of these receptors can cause bronchoconstriction (Everitt & Cairncross, 1969; Prime, Bianco, Griffin & Kamburoff, 1972; Simonsson, Svedmyr, Skoogh, Andersson & Bergh, 1972). This airways response to α -adrenoceptor stimulation is greatly enhanced in asthmatic patients and it is suggested that the increased bronchial α -adrenoceptor activity in asthma may result from a diminished β -adrenoceptor responsiveness to catecholamines (Patel & Kerr, 1973).

It is now well recognized that the β -adrenoceptor is the membrane bound enzyme, adenylyl cyclase, which on stimulation by β -adrenoceptor agonists catalyses the formation of cyclic adenosine monophosphate—cyclic AMP (Robison, Butcher & Sutherland, 1967). In guinea-pig trachea and human lung fragments a similar rise in cyclic AMP formation causes bronchial smooth muscle relaxation (Kaliner, Orange, Koopman, Austen & Laraia, 1971). Conversely, α -adrenoceptor stimulation which decreases cyclic AMP levels (Kaliner *et al.*, 1971) causes bronchoconstriction (Murad, 1973). In *in vitro* experiments α -adrenoceptor blocking drugs, phentolamine and thymoxamine, have been shown to potentiate the effect of isoprenaline resulting in increased cyclic AMP formation (Logson, Carnright, Middleton & Coffey, 1973; Alston, Patel & Kerr, 1974). In addition, these drugs can also restore diminished beta adreno-receptor function in patients with active asthma towards normal (Alston *et al.*, 1974). In light of above observations, I have examined the effect of thymoxamine alone and in combination with isoprenaline on the specific airways conductance in ten patients with extrinsic bronchial asthma.

Methods

Ten patients, aged between 18 and 43 years, with extrinsic bronchial asthma and reversible airways obstruction were investigated. All patients had positive prick tests to inhalant allergen and a blood eosinophil count of over 500 cells/mm³. Sodium cromoglycate therapy was discontinued for 70 days and simple bronchodilator drugs stopped 12-24 h before the tests. Informed consent was obtained in each case.

Airways resistance (Raw) was measured in a constant volume body plethysmograph (Dubois, Bothelho & Comroe, 1956) at a flow rate of 0.5 litre s⁻¹ while the patient panted at 2 Hz. Conductance, the reciprocal of Raw, was divided by the thoracic gas volume at which Raw was measured to give specific airways conductance (SGaw). The mean of four recordings was calculated to give the SGaw (s⁻¹ k Pa⁻¹).

Drugs used

Thymoxamine hydrochloride (15 g/litre, W.R. Warner & Co., Eastleigh, Hants., U.K.) and isoprenaline sulphate (10 g/litre, freshly prepared).

Procedure

After recording the baseline SGaw, each patient inhaled normal saline solution, thymoxamine (1 ml), isoprenaline (0.5 ml) or a mixture of isoprenaline (0.5 ml) and thymoxamine (1 ml) through a Wright's nebulizer using compressed air at a flow rate of 8 litres/minute. After each inhalation, SGaw was recorded at 5 min intervals for 30 minutes. The order of inhalations for each patient was randomized and he or she was unaware of the effects.

Results

The values of SGaw after saline, thymoxamine, isoprenaline and isoprenaline plus thymoxamine in ten patients are given in Tables 1, 2, 3 and 4. The mean baseline values of SGaw were different in each investigation, however, there was no statistical difference between them (paired *t*-test). Saline inhalation did not cause a significant change in SGaw. The mean SGaw increased by 43% after thymoxamine administration ($P < 0.05$). However, this increase was significantly less than the increase

in mean SGaw achieved with isoprenaline (122%, $P < 0.01$). When isoprenaline and thymoxamine were administered together the mean SGaw increased by 203% from the baseline value (Figure 1). There was a statistically significant difference between the bronchodilatation achieved with isoprenaline alone and that achieved with isoprenaline plus thymoxamine at 20, 25 and 30 min (paired *t*-test, $P < 0.05$). In one patient (No. 10) isoprenaline inhalation produced only a marginal increase in SGaw which lasted for 20 minutes. However, when this patient was treated

Table 1 Effect of saline on specific airways conductance (SGaw) in ten patients with extrinsic asthma

Subject number	Age (years)	Sex	Baseline	SGaw ($s^{-1}k Pa^{-1}$)					
				Time after saline inhalation (min)					
				5	10	15	20	25	30
1	27	M	0.64	0.75	0.69	0.72	0.77	0.80	0.78
2	28	F	0.84	0.78	0.82	0.74	0.74	0.80	0.77
3	19	M	0.60	0.72	0.68	0.66	0.62	0.63	0.69
4	21	F	1.38	0.93	1.03	1.35	1.35	1.14	1.23
5	24	F	1.13	1.20	1.08	1.20	1.25	1.13	1.16
6	18	M	0.62	0.74	0.60	0.69	0.75	0.80	0.78
7	37	M	0.92	0.98	1.12	1.06	0.80	1.11	0.94
8	23	F	1.32	1.40	1.29	1.34	1.39	1.42	1.39
9	32	M	1.10	1.01	0.92	1.01	0.96	1.05	1.09
10	41	M	0.40	0.38	0.42	0.36	0.39	0.42	0.45
Mean			0.90	0.89	0.87	0.91	0.90	0.93	0.93
s.e. mean			0.10	0.09	0.08	0.10	0.10	0.09	0.09
<i>t</i> -test				0.53	0.45	0.79	0.29	0.72	1.01
<i>P</i>				NS	NS	NS	NS	NS	NS

NS Not significant

Table 2 Effect of thymoxamine on specific airways conductance (SGaw) in ten patients with extrinsic asthma

Subject number	Baseline	SGaw ($s^{-1}k Pa^{-1}$)					
		Time after thymoxamine inhalation (min)					
		5	10	15	20	25	30
1	0.40	0.26	0.25	0.29	0.27	0.32	0.34
2	0.48	0.57	0.56	0.64	0.63	0.68	0.63
3	0.53	0.77	0.77	0.85	0.80	0.52	0.71
4	1.02	1.09	1.31	1.43	1.32	1.29	1.32
5	1.10	1.24	1.38	1.53	1.77	1.58	1.48
6	0.82	0.68	0.66	0.68	0.63	0.62	0.75
7	0.63	1.41	1.24	1.27	1.32	1.11	1.24
8	1.25	2.17	2.34	2.32	2.35	2.01	2.32
9	0.52	1.09	1.01	0.75	0.69	0.60	0.68
10	0.42	0.50	0.51	0.48	0.39	0.70	0.52
Mean	0.72	0.98	1.01	1.02	1.02	0.94	1.00
s.e. mean	0.08	0.17	0.19	0.19	0.21	0.17	0.19
<i>t</i> -test		2.22	2.36	2.62	2.32	2.37	2.58
<i>P</i> <		0.05	0.025	0.025	0.025	0.025	0.025

with a combination of isoprenaline and thymoxamine, there was a three-fold increase in his SGaw, and this improvement was maintained for more than 1 hour.

Discussion

In ten patients with asthma the α -adrenoceptor blocking drug, thymoxamine, when given by inhalation together with isoprenaline produced significantly greater bronchodilatation as compared to bronchodilatation achieved with isoprenaline alone. Further, in one of these patients (No. 10) isoprenaline alone produced only a marginal

increase in SGaw; however when this patient was treated with a combination of thymoxamine and isoprenaline a three-fold increase in his SGaw was noted. These results support the biochemical observations in which thymoxamine has been shown to potentiate the effect of β -adrenoceptor agonists and also to restore β -adrenoceptor responsiveness to isoprenaline in patients with acute asthma (Alston *et al.*, 1974). Said, Kitamura, Yoshida, Preskitt & Holden (1974) have reported a similar potentiation by phenoxybenzamine of isoprenaline induced bronchodilatation in guinea-pig tracheal preparations.

Thymoxamine is the most specific α -adrenoceptor blocking drug available for clinical use and

Table 3 Effect of isoprenaline on specific airways conductance (SGaw) in ten patients with extrinsic asthma

Subject number	Baseline	SGaw ($s^{-1}kPa^{-1}$)					
		Time after isoprenaline inhalation (min)					
		5	10	15	20	25	30
1	0.36	1.38	1.40	1.36	1.36	1.43	1.39
2	0.36	1.39	1.81	1.83	1.87	2.13	2.08
3	0.55	1.89	1.89	2.00	2.16	1.96	2.02
4	0.65	1.48	1.68	2.31	2.06	2.24	2.02
5	1.46	2.00	2.16	2.12	2.22	2.08	2.11
6	0.65	1.05	1.09	1.03	1.14	1.14	1.20
7	0.81	1.38	1.83	2.07	1.90	1.82	1.84
8	1.29	2.01	2.03	2.08	2.18	2.12	2.01
9	0.96	1.54	1.35	1.33	1.16	1.46	1.26
10	0.27	0.68	0.52	0.33	0.30	0.21	0.22
Mean	0.74	1.48	1.58	1.64	1.64	1.66	1.62
s.e. mean	0.13	0.13	0.16	0.20	0.20	0.14	0.19
t-test		4.25	3.95	3.19	2.75	3.31	3.13
P <		0.005	0.005	0.01	0.025	0.01	0.01

Table 4 Effect of isoprenaline + thymoxamine on specific airways conductance (SGaw) in ten patients with extrinsic asthma

Subject number	Baseline	SGaw ($s^{-1}kPa^{-1}$)					
		Time after isoprenaline + thymoxamine inhalation (min)					
		5	10	15	20	25	30
1	0.39	1.26	1.39	1.63	1.73	1.77	1.61
2	0.46	1.12	1.51	1.68	1.58	1.49	1.56
3	0.42	1.86	1.71	1.89	1.96	2.02	2.11
4	0.38	1.42	1.60	2.02	2.33	2.44	2.69
5	0.88	2.78	3.24	2.83	2.83	2.55	2.74
6	0.56	1.18	1.12	1.17	1.16	1.22	1.30
7	1.00	1.67	1.87	1.75	1.87	1.94	1.74
8	1.21	2.57	2.31	2.31	2.46	2.50	2.52
9	0.99	1.91	2.08	2.19	2.13	2.30	2.27
10	0.35	1.28	1.33	1.37	1.36	1.59	1.41
Mean	0.66	1.71	1.82	1.88	1.94	1.98	2.00
s.e. mean	0.10	0.18	0.19	0.15	0.16	0.14	0.17
t-test		8.09	7.81	9.59	9.26	10.49	8.55
P <		0.001	0.001	0.001	0.001	0.001	0.001

Figure 1 Effects of saline (●), thymoxamine (○), isoprenaline (▲) and isoprenaline + thymoxamine (■) on the mean SGaw in ten patients with extrinsic asthma.

its action is competitive with noradrenaline and thus reversible (Brownlee, 1966). Unlike phenolamine and phenoxybenzamine it lacks blocking action against angiotensin and 5-hydroxytryptamine (Birmingham & Szolcsanyi, 1965). Thymoxamine given by inhalation does not significantly affect the pulse rate or blood pressure and it is therefore unlikely that significant systemic blood levels of thymoxamine are attained

to release adrenaline from adrenal medulla and other storage sites as has been reported with phentolamine (Lish, Robbins & Dungan, 1968).

It has recently been suggested that bronchomotor tone is dependent on intracellular levels of cyclic AMP (Reed, 1974). Asthmatic patients show changes in adenylyl cyclase-cyclic AMP system related to the severity of their asthma (Parker & Smith, 1973; Alston *et al.*, 1974; Patel, Alston & Kerr, 1974) and it is possible that similar enzymatic changes in the bronchial smooth muscle cause variability of bronchomotor tone in these patients. It has been shown that in acute asthma, the β -adrenoceptor system is maximally stimulated by endogenous factors so that further stimulation becomes increasingly difficult (Patel *et al.*, 1974). In this situation, α -adrenoceptor blocking drugs have been shown to restore adenylyl cyclase responsiveness to β -adrenoceptor agonists resulting in increased cyclic AMP formation (Alston *et al.*, 1974). A similar effect of thymoxamine in the bronchial smooth muscle would explain the results reported. In addition, thymoxamine inhibits histamine, allergen and exercise induced bronchoconstriction (Bianco, Griffin, Kamburoff & Prime, 1972; Patel & Kerr, 1975; Patel, Kerr, MacDonald & McKenzie, 1976) and this effect of thymoxamine is possibly mediated by its ability to increase cyclic AMP formation. These observations of α -adrenoceptor blocking drugs in asthma suggest that they may have a place in management of chronic labile airways obstruction. However, carefully conducted clinical trials will be required to evaluate therapeutic significance of this form of therapy.

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