Thymoxamine: lack of antihistaminic effects in clinical doses in man

S. AL-DAMLUJI, A. GROSSMAN, ¹P. TURNER & G. M. BESSER

Departments of Endocrinology and ¹Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE

The purpose of this study was to investigate whether the α_1 -adrenoceptor antagonist thymoxamine possesses antihistaminic activity in clinical doses in man, as has been reported on the guinea pig ileum *in vitro*. Five normal subjects were given on three separate occasions intravenous infusions of thymoxamine (0.15 mg kg^{-1} loading dose followed by $0.15 \text{ mg kg}^{-1} \text{ h}^{-1}$), chlorpheniramine (1.5 mg loading dose followed by 1.5 mg h^{-1}) and normal saline (placebo). Intravenous bolus doses of histamine (1 and $2 \mu\text{g kg}^{-1}$) were given after pretreatment with propranolol 10 mg to block the β -adrenoceptor agonist effects of the catecholamines released by the histamine injections. Histamine caused a dose-dependent reduction of FEV₁ and FVC that was antagonised by chlorpheniramine but not by thymoxamine, suggesting that thymoxamine has no antihistaminic activity in the doses used in man. Thymoxamine caused a small enhancement of the bronchoconstrictor effect of the lower dose of histamine. The relatively selective action of thymoxamine makes it a suitable agent for the investigation of α_1 -adrenoceptors.

Keywords thymoxamine histamine lung function antihistamines

Introduction

Thymoxamine is one of the most highly selective available antagonists at postsynaptic α_1 -adrenoceptors (Drew, 1976). It is a competitive antagonist of noradrenaline *in vitro* and has no agonist activity when given even in very large doses *in vivo* (Birmingham & Szolcsanyi, 1965; Birmingham *et al.*, 1967). The drug has no β -adrenoceptor or serotonergic antagonist action (Birmingham & Szolcsanyi, 1965) and no significant α_2 -adrenoceptor antagonist activity (Drew, 1976). It is more lipid soluble than endogenous catecholamines and is able to penetrate the blood brain barrier (Wada *et al.*, 1982). These properties of thymoxamine make it an extremely useful tool for the investigation of central and peripheral adrenergic and noradrenergic systems in man. Apart from its α_1 -adrenoceptor antagonist activity, the only other known pharmacological effect of thymoxamine is a weak H₁-antihistaminic action on the guinea pig ileum *in vitro* (Birmingham & Szolcsanyi, 1965) but it is unclear whether

this effect is relevant in the doses used in human subjects. The purpose of this investigation was to examine whether thymoxamine in the doses commonly used has any antihistaminic activity and the model that we have chosen is the bronchoconstrictor effect of intravenously injected histamine in normal man.

An intravenous bolus injection of histamine in normal subjects causes a small, transient increase in airways resistance that is maximal at 30 to 60 s (Newball & Keiser, 1973). The rapid reversal of the airways obstruction may be due to the release of catecholamines that is caused by the histamine injection (Smith *et al.*, 1985), causing a compensatory bronchodilator effect. In support of this suggestion is the fact that intravenous histamine injections cause more pronounced bronchoconstriction in adrenalectomised than normal cats (Colebatch & Engel, 1974) and that pre-treatment

with propranolol enhances the bronchoconstrictor effects of histamine in normal man (Ploy-Song-Sang *et al.*, 1978). The release of catecholamines by histamine may explain why continuous intravenous infusions of histamine in normal subjects are not usually followed by any consistent change in airways resistance (Brown *et al.*, 1977; Ploy-Song-Sang *et al.*, 1978). Vasodilatation caused by thymoxamine may also release catecholamines by a reflex mechanism. In order to eliminate the antagonistic effects of the released catecholamines, we pretreated our subjects with propranolol.

Methods

Five medically qualified normal volunteers who were members of the department were studied on three occasions each at weekly intervals, at the same time of day for each subject. The subjects lay in bed in a semi-recumbent position in a quiet room with electrocardiographic monitoring. Thirty minutes after the placing of a forearm venous cannula, the following infusions were given in single (subject) blind, random order for 70 min:

1. Normal saline bolus followed by a continuous infusion
2. Thymoxamine 0.15 mg kg⁻¹ bolus followed by 0.15 mg kg⁻¹ h⁻¹
3. Chlorpheniramine 1.5 mg bolus followed by 1.5 mg h⁻¹

Twenty minutes after the commencement of the continuous infusions, the subjects received propranolol 10 mg over 10 min intravenously. At the end of the propranolol infusion the subjects were given histamine acid phosphate 1 µg kg⁻¹ (of the base) and a 2 µg kg⁻¹ bolus was given at 50 min.

Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured with a Vitalograph dry spirometer at 10 min intervals during the control period, at 30 s intervals for 3 min following each histamine injection and at 5 min intervals thereafter. The coefficients of variation of ten replicate measurements in two subjects were: FEV₁: 0.6% and 1.85%; FVC: 1% and 1.1%. The heart rate was calculated from the electrocardiogram and blood pressure was measured by sphygmomanometry (phases 1 and 5).

The data are expressed as the mean ± s.e mean. Statistical examination was by analysis of covariance and individual time points were compared by Student's *t*-test.

Results

FEV₁ and FVC prior to the onset of the saline, thymoxamine and chlorpheniramine infusions were: 3640 ± 195 and 4090 ± 183; 3630 ± 224 and 4140 ± 238; 3570 ± 222 and 3980 ± 217 ml respectively, and were not significantly different from each other. There were small falls in FEV₁, FVC and heart rate following propranolol during all three infusions and these reached statistical significance for heart rate during the thymoxamine and chlorpheniramine infusions and FEV₁ during the chlorpheniramine infusion (*P* < 0.05, Student's *t*-test).

The histamine injections were followed by dose-dependent reductions in FEV₁ and FVC (Figure 1 and Table 1). The chlorpheniramine infusion was accompanied by smaller falls in FEV₁ and FVC than during the saline infusion following both doses of histamine. There was no attenuation of the falls in FEV₁ or FVC during the thymoxamine infusion compared with saline. The mean maximum histamine-induced falls in FEV₁ and FVC were greater during the thymoxamine infusion than during saline (Table 1), but the differences were only significant for FVC following the 1 µg kg⁻¹ dose of histamine. The differences between thymoxamine and saline were not significant by analysis of covariance.

Mean heart rate was slightly faster during the thymoxamine infusion than during chlorpheniramine and saline, but the differences were not statistically significant. Neither drug had any significant effect on blood pressure in comparison with saline. The subjects experienced a metallic taste, headache and facial flushing following the histamine injections. No arrhythmias or hypotensive episodes were observed.

Discussion

The bronchoconstrictor effect of histamine was inhibited by the H₁-receptor antihistamine chlorpheniramine, confirming that it is mediated by an H₁-receptor histaminic effect. Thymoxamine did not attenuate histamine induced bronchoconstriction, suggesting that the previously observed H₁-antihistaminic effect *in vitro* is not relevant in man, in the doses used clinically. The dose of thymoxamine used in this study produces effective blockade of α₁-adrenoceptors; similar doses abolish the cardiovascular and hormonal responses to the α₁-adrenoceptor agonist methoxamine and significantly reduce the pituitary-adrenal responses to some physiological stimuli, which is compatible with blockade of α₁-adrenoceptors (Al-Damluji *et al.*,

Figure 1 The effects of thymoxamine, chlorpheniramine and saline on the bronchoconstrictor action of intravenous histamine in five normal subjects. The three infusions were given throughout the study period and propranolol 10 mg was given from 20 to 30 min. The FEV₁ and FVC data are expressed as the percentage of the value at 0 min and only standard error bars greater than 2% are shown. ○ thymoxamine 0.15 mg kg⁻¹ bolus + 0.15 mg kg⁻¹ h⁻¹, ▲ chlorpheniramine 1.5 mg kg⁻¹ bolus + 1.5 mg h⁻¹, ● saline.

Table 1 The relationship of histamine dose to bronchoconstrictor action, expressed as the percentage change in FEV₁ and FVC from the values immediately preceding the histamine injection. Values are means ± s.e. mean

Infusion	Histamine dose (µg kg ⁻¹)	Percentage change in FEV ₁	Percentage change in FVC
Saline	1	-6.0 ± 1.2	-5.0 ± 1.8
	2	-9.4 ± 1.6	-9.5 ± 1.1
Chlorpheniramine	1	-0.3 ± 2.0	+1.0 ± 2.5
	2	-4.6 ± 1.2	-4.5 ± 1.1*
Thymoxamine	1	-7.8 ± 0.4	-9.4 ± 0.7*
	2	-9.7 ± 2.4	-11.4 ± 2.2

* $P < 0.05$, Student's t -test vs equivalent histamine dose during saline infusion.

1987a,b,c). The mechanism of the slight enhancement by thymoxamine of the bronchoconstrictor action of histamine may be due to bronchoconstrictor α_1 -adrenoceptor activation by endogenous catecholamines, released as a reflex effect to thymoxamine-induced vasodilatation (Mathe *et al.*, 1971). Pretreatment with propranolol would be expected to block the bronchodilator effects of the released catecholamines, but the blockade of bronchial α_1 -adrenoceptors

with thymoxamine may have been incomplete. An effect of thymoxamine on the metabolic clearance of histamine is also possible.

Investigations of the interaction of α -adrenoceptor antagonists and histamine in asthmatic patients have yielded conflicting results. Kerr *et al.* (1970) found that intravenous injections of phentolamine and phenoxybenzamine inhibited the bronchoconstrictor response to intravenous histamine in asthmatic subjects, but Pegelow

(1974) could not confirm these findings using inhaled phentolamine. The effects of phentolamine and phenoxybenzamine are difficult to interpret in view of their multiple actions; in addition to their antihistaminic effects, the α_2 -adrenoceptor antagonist activity of phentolamine in particular may release endogenous catecholamines, resulting in bronchodilatation by activating bronchial β -adrenoceptors, which are not blocked by these two antagonists. Phentolamine does not inhibit the bronchoconstrictor effects of histamine on human bronchial muscle *in vitro* (Mathe *et al.*, 1971), confirming that the effects of phentolamine *in vivo* may be exerted indirectly, possibly via α_2 -adrenoceptors. Thymoxamine does not have significant α_2 -adrenoceptor antagonist activity (Drew, 1976), but α_1 -adrenoceptor antagonism causes vasodilatation, resulting in release of catecholamines. Thus the findings by previous investigators that

thymoxamine attenuated the bronchoconstrictor effects of inhaled histamine may be explicable on the basis of release of endogenous catecholamines caused by the vasodilatation following the administration of thymoxamine, that is apparent on examining their data (Gaddie *et al.*, 1972; Bianco *et al.*, 1972). This problem was avoided in our studies by pretreating the subjects with propranolol, to block the β -adrenoceptor effects of endogenous catecholamines.

In summary, our data provide no evidence for a major antihistaminic effect of thymoxamine in clinical doses. The drug should be a useful agent in the investigation of α_1 -adrenoceptor mechanisms in man, in view of its relatively selective actions.

S. Al-Damluji was a Medical Research Council Training Fellow.

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(Received 3 December 1986,
accepted 17 February 1987)