Effects of H₁-receptor blockade with terfenadine in nocturnal asthma

C. TEALE, J. F. J. MORRISON & S. B. PEARSON

Pulmonary Function Laboratory, Killingbeck Hospital, York Road, Leeds, LS14 6UQ

- 1 In a single-blind placebo controlled study we have measured peak flow (PEFR) at 04.00 h and 16.00 h in eight asthmatics 6 h after placebo or terfenadine 120 mg, to determine if diurnal variation in histamine mediated effects contribute to nocturnal bronchoconstriction in asthma.
- 2 On placebo there was a significant diurnal variation in mean PEFR of 41 l min⁻¹ ($P < 0.05$). Terfenadine improved 04.00 h baseline mean PEFR from 242 to 278 l min⁻¹ ($P < 0.05$) but a 38 l min⁻¹ diurnal variation in mean PEFR persisted ($P < 0.05$).
- 3 We conclude that H₁-receptor blockade with terfenadine may produce modest nocturnal bronchodilatation but does not influence the diurnal variation in PEFR in asthma suggesting that H₁-receptor mediated effects are not important in the pathogenesis of nocturnal asthma.

Keywords nocturnal asthma terfenadine histamine

Introduction

Diurnal variation in airflow obstruction is well recognised in asthma (Hetzel & Clark, 1980) and can lead to deteriorating symptoms and even death. The precise cause of nocturnal asthma remains uncertain although a number of factors probably contribute (Barnes, 1984). We have previously shown that vagal blockade with atropine corrects most but not all of the night time fall in PEFR in asthma suggesting that diurnal variation in vagal tone is important in nocturnal asthma but that other factors are likely to be involved as well (Morrison *et al.*, 1988, 1990). Histamine is an important mediator in the pathogenesis of asthma, stimulating bronchoconstriction by several mechanisms (White & Kaliner, 1988; White *et al.*, 1987). Plasma concentrations of histamine have been shown to peak at 04.00 h when nocturnal bronchoconstriction is most marked (Barnes *et al.*, 1980) suggesting a possible role for histamine in nocturnal asthma. In this single-blind placebo controlled study we have given the H₁-receptor antagonist terfenadine to subjects with documented nocturnal deterioration in their asthma to investigate whether histamine mediated effects contribute to nocturnal bronchoconstriction.

Methods

Eight asthmatics with a diurnal variation in PEFR of greater than 20% for more than 70% of the time on home PEFR monitoring were admitted to hospital for one night of acclimatisation followed by 2 study days.

Oral bronchodilators were omitted for 2 days before admission and tea and coffee were not allowed during the study. Inhaled and oral steroids were continued, but inhaled bronchodilators were omitted for 10 h before each study session. On the first study day subjects were given placebo tablets at 22.00 h and then woken at 04.00 h when PEFR, best of three, was recorded using a Wright peak flow meter. At 10.00 h they received placebo tablets and PEFR was measured at 16.00 h. The procedure was repeated the following day except that oral terfenadine 120 mg was given instead of placebo. Results were analysed by paired *t*-tests.

The antihistamine terfenadine was chosen because it does not produce the anticholinergic side effects of earlier antihistamines such as chlorpheniramine (Holgate *et al.*, 1985) and has been shown not to influence methacholine induced bronchoconstriction (Wood-Baker & Holgate, 1990). Terfenadine has a half-life of 12 h (White *et al.*, 1987) and was given 6 h before PEFR measurements to allow undisturbed sleep between retiring and the 04.00 h study session. The 120 mg dosage of terfenadine was chosen because it was used in an earlier study on atopic asthmatics (Cookson, 1987) where it had a bronchodilator action approaching that of 200 µg of inhaled salbutamol. A single-blind non-randomised protocol was used to allow terfenadine to be given on the second study day and thus avoid the need for a prolonged washout period. The study was approved by the Leeds Eastern Health Authority Ethics Committee and verbal informed consent obtained from each subject.

Table 1 Subject details

Age (years)	Sex	Duration of asthma (years)	Atopy	Smoking	Medication	FEV ₁ (l)	(% predicted)
40	M	26	—	—	IB,I+OS	1.5	(41%)
68	F	2	—	+	IB,IA,IS	0.6	(33%)
72	M	2	—	—	IB,IS,T	1.0	(37%)
67	M	2	—	—	IB,IA,IS,T	1.3	(52%)
29	M	19	+	+	IB,IS	3.6	(87%)
64	M	3	—	+	IB,IA,T	1.2	(48%)
66	M	2	—	+	IB,IA,IS	2.0	(74%)
55	F	6	—	+	IB,IA,I+OS,T	1.4	(60%)

Medication: IB = inhaled β_2 -adrenoceptor agonists; IA = inhaled anticholinergics; IS = inhaled steroids; OS = oral steroids; T = theophyllines.

Results

Details of subjects are shown in Table 1, they had a mean age of 58 years (range 29–69 years) and a mean baseline FEV₁ of 1.54 l (range 0.5 to 4.2 l) or 49% predicted (range 33% to 87% predicted). Only one subject was atopic. The results are summarised in Figure 1.

On placebo mean baseline PEFR rose from 242 l min⁻¹ at 04.00 h to 283 l min⁻¹ at 16.00 h, a significant diurnal variation of 41 l min⁻¹ or 17% ($P < 0.05$). Terfenadine increased mean baseline nocturnal PEFR from 242 l min⁻¹ to 278 l min⁻¹ ($P < 0.05$) but a significant diurnal variation in mean PEFR of 38 l min⁻¹ (14%) remained ($P < 0.05$).

Hence in these moderately severe asthmatics who showed significant nocturnal bronchoconstriction terfenadine produced a modest bronchodilatation at

night and during the daytime but did not influence the magnitude of the nocturnal dip.

Discussion

This is the first study to examine responses to an H₁-receptor blocking drug at night in asthmatics with nocturnal dipping. In our eight subjects terfenadine 120 mg produced an increase in mean PEFR, 6 h after administration, of 15% at night and 12% during the daytime but failed to influence the nocturnal dip which remained at 38 l min⁻¹ compared with 41 l min⁻¹ on placebo. This suggests a modest bronchodilator action for terfenadine in these asthmatics causing a shift in baseline, but its failure to influence the nocturnal dip is against a direct role for H₁-receptor mediated effects in nocturnal asthma.

Cookson (1987) reported a 30% increase in expiratory flow at 25% of vital capacity in seven atopic asthmatics with normal lung function 2 h after terfenadine 120 mg. Two outpatient studies have examined the effects of H₁-receptor blockade on morning and evening PEFR measurements in mild extrinsic asthmatics who did not demonstrate a significant diurnal variation in PEFR; both showed an improvement in morning and evening PEFR (Gould *et al.*, 1988; Taytard *et al.*, 1987).

Our results, in asthmatics with reduced baseline lung function and largely non-atopic status, suggest that terfenadine has a bronchodilator action at night as well as in the daytime, although such a conclusion must be guarded as the study was not specifically designed to examine for its possible bronchodilator actions.

Two points need to be considered in assessing these results. Firstly, we adopted a non-randomised protocol to avoid the need for a prolonged wash out period. This raises the possibility of an order effect; however, previous studies by ourselves on nocturnal asthma showed no evidence of an order effect (Morrison *et al.*, 1988, 1989,

Figure 1 Nocturnal asthma: effect of placebo and terfenadine on 04.00 h and 16.00 h PEFR in eight asthmatics (means + s.e. mean).

1990). Secondly, with only eight subjects, a significant effect could have been missed due to type 2 error.

In conclusion this study shows that although H_1 -receptor blockade with terfenadine may produce

nocturnal as well as daytime bronchodilatation it does not exert a direct effect on nocturnal dipping suggesting that histamine mediated effects do not contribute to nocturnal bronchoconstriction in asthma.

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