Br. J. clin. Pharmac. (1982), **13**, 321S–323S

INFLUENCE OF INTRINSIC SYMPATHOMIMETIC ACTIVITY (ISA) DURING β-ADRENOCEPTOR BLOCKADE IN ASTHMATICS

P. DOROW

Department of Cardiology and Pulmology, Universitätsklinikum Charlottenburg, Spandauer Damm 130, D-1000 Berlin 19, West Germany

1 Ten patients suffering from extrinsic bronchial asthma were examined.

2 In the pretreatment period, the histamine concentration required to produce a 20% decrease of forced expiratory volume in one second (FEV_1) was 7.71 mg/ml.

3 Histamine provocation was repeated 2 h after administration of placebo, propranolol 40 mg, pindolol 5 mg or metoprolol 50 mg. After pindolol and metoprolol the histamine concentrations were slightly, but not significantly, lower than after placebo. After propranolol only 3.16 mg/ml histamine was necessary to reduce FEV_1 by 20%.

4 This indicates that in equipotent cardiac β-adrenoceptor blocking doses, in contrast to propranolol, neither pindolol nor metoprolol increased sensitivity to the bronchoconstrictor effects of inhaled histamine.

Introduction

Although β-adrenoceptor antagonists are widely used for the treatment of hypertension and coronary heart disease, the presence of chronic obstructive lung disease may be a factor limiting the use of these drugs in certain patients. In such patients it is claimed that β-adrenoceptor blocking agents with marked intrinsic sympathomimetic activity or those showing a relative selectivity for β_1-adrenoceptors may be less likely to produce undesirable bronchial side effects than antagonists lacking these properties.

It is known that patients with chronic obstructive lung disease show an increased reactivity to inhaled histamine and this investigation was carried out to determine the effects of β-adrenoceptor blockade on the sensitivity to inhaled histamine in patients with mild extrinsic bronchial asthma.

Methods

Ten patients (nine male, one female) with a mean ± s.d. age of 38.5 ± 8.3 years (range 28–63 years) were studied. Their height was between 162 and 188 cm (mean ± s.d. 178.5 ± 10.4 cm). With all these patients an extrinsic bronchial asthma had been verified by an intra-cutaneous allergy test. Only those patients were chosen who at the time of examination, showed normal or only slightly obstructed ventilation. During the 24 h preceding the examination, the patients were not given any sympathomimetics, anticholinergics, xanthine derivatives, antihistamines or cortisone preparations. In all patients a decrease in forced expiratory volume in one second (FEV_1) by approximately 20% was produced by inhalation of a histamine spray. The patients received, with a 3 day interval between treatments, placebo, pindolol 5 mg, metoprolol 50 mg or propranolol 40 mg, in a randomized design. The histamine test was carried out before and 2 h after administration of the treatments. The doses of β-adrenoceptor blocking drugs used were those which would produce equipotent cardiac β-adrenoceptor blockade.

After determining the FEV_1, the patients inhaled an isotonic phosphate buffer solution (pH 6.9) for 90 s and at the end of inhalation, the FEV_1 was redetermined. Histamine was then inhaled for 2 min, every 5 min. The inhalation was administered via a mouthpiece with the nose closed. The histamine concentration was between 0.25 and 32 mg/ml and the test was stopped when the FEV_1 was reduced by approximately 20%. The % decrease in FEV_1 was calculated from the FEV_1 after inhalation of isotonic phosphate buffer solution (FEV_1 a) and the lowest value of FEV_1 (FEV_1 b) after histamine inhalation:

$$100 \times (FEV_1, a - FEV_1\ b)/FEV_1\ a$$

The histamine concentration required to decrease FEV_1 by 20% (PC_{20}) was noted.

0306–5251/82/130 321–03 $01.00

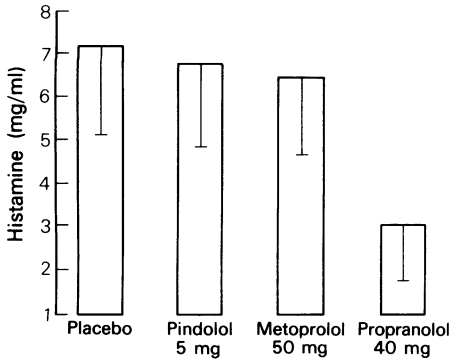

Figure 1 Effect of β-adrenoceptor blockers on PC_{20} histamine concentration (mean ± s.d.).

Results

Before treatment, the concentration of histamine necessary to produce a 20% decrease in FEV_1 was 7.71 ± 3.9 mg/ml (mean ± s.d.) (Figure 1) and a similar value was obtained after placebo administration. The concentrations of histamine required were slightly, but not significantly, lower after pindolol (mean ± s.d. 6.8 ± 3.9 mg/ml) and metoprolol (mean ± s.d. 6.5 ± 3.7 mg/ml). In contrast administration of propranolol was associated with a significant decrease in the histamine concentration to produce a 20% reduction in FEV_1 to 3.16 ± 2.7 mg/ml. Statistical analysis using Duncan's new multiple range test showed a significant difference between propranolol and the other β-adrenoceptor blocking drugs with a probability of 96%. Two hours after the administration of propranolol, before the histamine provocation test, there was a significant fall in FEV_1 (Figure 2) which was not observed after treatment with pindolol or metoprolol.

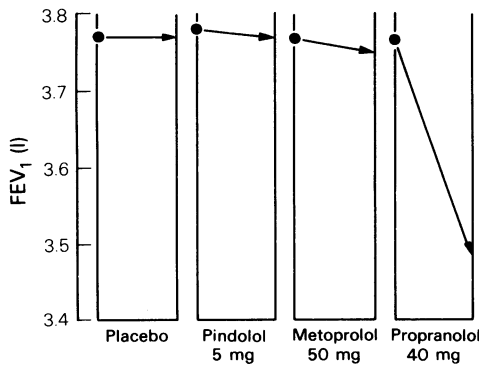

Figure 2 Effect of β-adrenoceptor blockers on forced expiratory volume in one second (FEV_1). FEV_1 was measured before and 2 h after administration of the drugs.

Discussion

The inhaled histamine-provocation test represents a sensitive method for assessing bronchial hyperreactivity. It is believed that histamine and other mediators partake in the pathogenesis of bronchial asthma, although the associations are not fully clarified. The bronchial hyper-reactivity of these patients was evidenced by a decrease of the FEV_1 after inhalation of a mean histamine-concentration of 7.71 mg/ml. On another test-day 2 h after placebo administration, the mean histamine concentration required to reduce FEV_1 by 20% was 7.40 mg/ml. Thus the bronchial reactivity had not changed substantially during the observation period. However 2 h after 40 mg propranolol there was a distinct increase in bronchial reactivity as shown by the significant decrease in histamine concentration necessary to reduce FEV_1 by 20%.

Two hours after administration of propranolol the histamine concentration necessary to reduce FEV_1 by 20% was 57.8% lower than that required in the pretreatment period. In similar experiment in which a larger dose of propranolol (80 mg) was used, Ruffin *et al.* (1979) found that the histamine concentration needed to produce a 20% reduction in FEV_1 was 47.8% lower than that necessary before treatment. The difference between the results of these authors and those reported here is probably attributable to differences in the sensitivities of the patients participating in the two studies. In contrast to the present study where a histamine concentration of 7.4 mg/ml was necessary to reduce FEV_1 by 20% in the pretreatment period, in their patients, Ruffin *et al.* (1979) were able to illicit the same response with a histamine concentration of 3.7 mg/ml.

In this study we were unable to confirm the results of Ruffin *et al.* (1979) who found that after administration of metoprolol (100 mg) in asthmatic patients the bronchial sensitivity to histamine was significantly increased.

However, this difference is probably due to the fact that in the present study a lower dose (50 mg) of metoprolol was employed. In our experiments pindolol (5 mg) and metoprolol (50 mg) both caused a slight increase in the bronchial sensitivity to histamine but this effect was not statistically significant.

Histamine produces an increase in airways resistance and a decrease in compliance (Nadel, 1973) and the results of animal experiments reveal that these effects are inhibited by pretreatment with atropine suggesting that they are not due to a direct effect on bronchial smooth muscle (Drazen & Austen, 1974) but are indirectly mediated. The results presented here suggest that propranolol increases the sensitivity to inhaled histamine by virtue of its β_2-adrenoceptor blocking effects. Pindolol, presumably

because of its pronounced ISA, and at the dose used here the relatively β_1-selective antagonist metoprolol, do not potentiate the bronchoconstrictor effects of histamine.

I thank the patients who participated in the study, and Dr H. Letzel for statistical analysis.

References

DRAZEN, J.M. & AUSTEN, K.F. (1974). Effects of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and pulmonary mechanics interalteration by atropine. *Fed. Proc.*, **33**, 576 a.

NADEL, J.H. (1973). Neurophysiologic aspects of asthma. In *Asthma: Physiology, Immunopharmacology and treatment.* pp. 29–38. New York: Academic Press.

RUFFIN, R.E., FRITH, P.A., ANDERTON, R.C., KUMANA, C.R., NEWHOUSE, M.T. & HARGREAVE, F.E. (1979). Selectivity of beta adrenoreceptor antagonist drugs assessed by histamine bronchial provocation. *Clin. Pharmac. Ther.*, **25**, 536–540.