Br. J. clin. Pharmac. (1986), **21**, 234–237

Bronchodilator activity of a new inhaled β_2-adrenoceptor agonist, tulobuterol and its protective effect in exercise-induced asthma

K. R. PATEL
Department of Respiratory Medicine, Western Infirmary, Glasgow G11 6NT

In fifteen patients with asthma tulobuterol, a new β_2-adrenoceptor agonist, given by inhalation in 100 μg increments up to a cumulative dose of 600 μg produced dose related increases in both the FEV_1 and FVC. The bronchodilation was observed within 5 min of the first dose. In a further nine patients tulobuterol 200 μg and 400 μg aerosol inhibited exercise-induced asthma following 6–8 min treadmill exercise and the effect was comparable to 200 μg salbutamol aerosol. Minor muscle tremors were observed in two patients with 400 μg of tulobuterol but no significant changes in pulse rate or blood pressure were noted.

Keywords β_2-adrenoceptor bronchodilator tulobuterol exercise asthma

Introduction

Tulobuterol (α- [(tert-butylamino) methyl]-*o*-chlorobenzyl alcohol hydrochloride) is a new synthetic β_2-adrenoceptor agonist with a potent and prolonged bronchodilator activity in both man and animals (Kubo *et al.*, 1975, 1977; Shiota & Kuriharu, 1978; Massen *et al.*, 1983) when given orally. In a comparative study of salbutamol and tulobuterol given orally, the bronchodilator activity of tulobuterol was found to be significantly longer (Shiota & Kuriharu, 1978). The effect of inhaled tulobuterol has not been studied previously. Fifteen patients with chronic stable asthma were studied to determine the bronchodilator activity and effective dose of tulobuterol aerosol. In a further nine patients with exercise-induced asthma the protective effect of 200 μg salbutamol aerosol was compared to 200 and 400 μg tulobuterol aerosol in a double-blind placebo controlled study.

Methods

Bronchodilator activity

Fifteen patients aged 27–62 years (mean 47.3 years) with chronic stable asthma were studied. The pretreatment forced expiratory volume in 1 s (FEV_1) values were < 70% of their predicted normal values and all patients demonstrated an improvement in FEV_1 of greater than 20% at 15 min after inhalation of 200 μg salbutamol from a metered dose inhaler (MDI). The study was approved by the hospital ethics committee and informed consent was obtained from each patient.

The forced expiratory volume in 1 s (FEV_1) and the forced vital capacity (FVC) were measured on a dry wedge spirometer (Vitalograph) and the best of three attempts was taken for analysis. Systolic and diastolic blood pressures (BP) and pulse rate were monitored at 5 min

Correspondence: Dr K. R. Patel, Department of Respiratory Medicine, Western Infirmary, Glasgow G11 6NT

intervals using an electronic BP monitor (EME Model 3100, EME Ltd, 17 Bristol Gardens, Brighton, BN2 5JR, UK) with the patient seated in a chair. Each subject attended between 08.30 and 09.00 h, having stopped bronchodilator therapy for at least 12 h. After obtaining stable baseline FEV_1, FVC, pulse and BP each patient received a placebo inhalation from a MDI and the measurements were repeated 10 min later. If no significant changes in spirometric measurements were noted, the dose-ranging study was commenced. The patient inhaled 100 μg tulobuterol (1 puff) from a MDI (Bremax®, Abbott International, Chicago, USA). Spirometry, BP and pulse rate were recorded at 5 min intervals for 40 min or until the FEV_1 reached a plateau. The patient was given a further 100 μg tulobuterol and the procedure repeated till a cumulative dose of 600 μg tulobuterol was given or the patient developed significant side effects requiring termination of the study. The changes in FEV_1 and FVC (absolute and percentage increases) were calculated from post-placebo baseline and analysed using Student's paired *t*-test (Figure 1 for data).

Effects on exercise asthma

A further nine patients with extrinsic and exercise asthma aged 19–46 years were studied. All patients had a FEV_1 greater than 80% of their predicted normal. Sodium cromoglycate was stopped for 3 days and inhaled bronchodilator drugs for at least 12 h. Exercise testing consisted of steady state running on an inclined treadmill (10°) for 6–8 min and was carried out as described previously (Patel, 1981). The study was carried out in a random double-blind fashion using the double dummy technique. The treatment consisted of either placebo, 200 μg or 400 μg tulobuterol or 200 μg salbutamol and patients exercised 20 min later. Spirometry was repeated 20 min after each treatment; then at 2, 5, 10, 15 and 30 min post-exercise. The results of the tests were expressed as the mean maximal percentage fall in FEV_1 from the baseline at 20 min after treatment and analysed by Student's *t*-test (Figure 2).

Results

Bronchodilator activity

The mean pre- and post-placebo baseline FEV_1 values were 1.31 l (49.2% of the predicted) and 1.29 l, respectively, in 15 patients. Placebo aerosol did not cause a significant change. The mean maximal percentage increase in the FEV_1

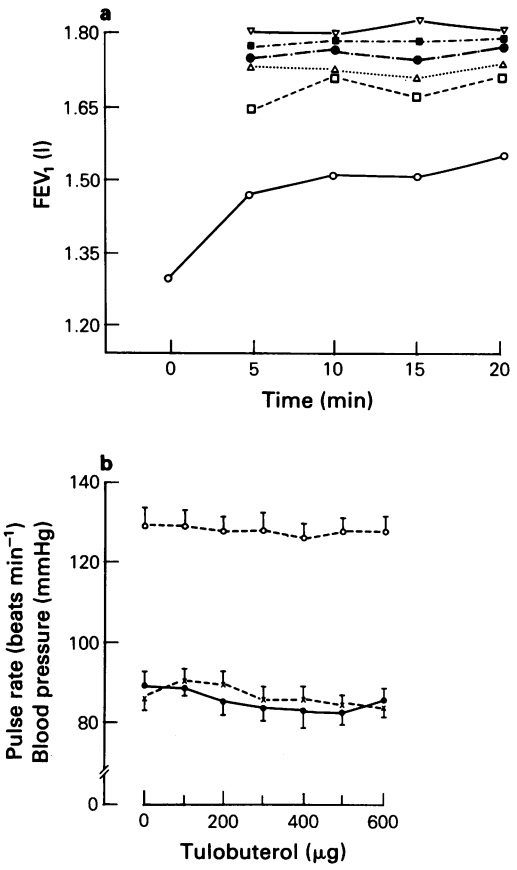

Figure 1 The effect of placebo and cumulative dosing of tulobuterol (○, 100 μg; □, 200 μg; △, 300 μg; ●, 400 μg; ■, 500 μg; ▲, 600 μg) on (a) the mean FEV_1 and (b) pulse rate (●—●) and blood pressure (○--○, systolic, x---x, diastolic) in 15 patients with asthma.

(± s.e. mean) and FVC after 100 μg was 36.9 (19.1) and 32.9 (7.9), respectively, ($P < 0.01$). In six patients spirometric measurements were carried out at 1 and 3 min after 100 μg tulobuterol and three of these patients showed an improvement in FEV_1 of greater than 15% just 1 min after dosing, whereas all six showed an improvement in FEV_1 of 15% by 3 min. There was a dose-related increase in the FEV_1 (Figure 1). The improvement in FEV_1 with 200 μg tulobuterol was significant compared to 100 μg tulobuterol, but no significant difference was observed between 200 μg and 300 μg, 400 μg and 500 μg tulobuterol. Tulobuterol 600 μg gave a small but significant improvement in FEV_1 when compared with 500 μg ($P < 0.05$). Two patients did not show a significant bronchodilator response to tulobuterol. The effect of tulobuterol on pulse

rate and blood pressure was not significant (Figure 1). Two patients showed clinical evidence of tremors after the fourth dose; however, all patients were able to complete the study.

Effects on exercise-induced asthma

There was no significant difference in the pre-treatment baseline FEV_1 on four days of testing. Placebo had no effect whereas tulobuterol and salbutamol both produced significant improvement in FEV_1 there being no difference between active treatments. Salbutamol and 200 μg and 400 μg tulobuterol significantly inhibited exercise-induced falls in FEV_1 ($P < 0.001$; Figure 2). The inhibitory effects of salbutamol and tulobuterol were comparable and no statistical differences were observed between active treatments. The changes (s.e. mean) in pulse rate after 200 μg salbutamol and 200 μg and 400 μg tulobuterol were 2(2), 3(3), 3(4) beats min^{-1}, respectively. The changes in systolic blood pressure (mm Hg) after salbutamol, and tulobuterol 200 and 400 μg were +2(2.3), +4(2.3), +3(2.3), respectively, and the changes in diastolic blood pressure were −1(3.3), 0(1.5) and −2(3.2), respectively. The changes in pulse and blood pressure were not significant.

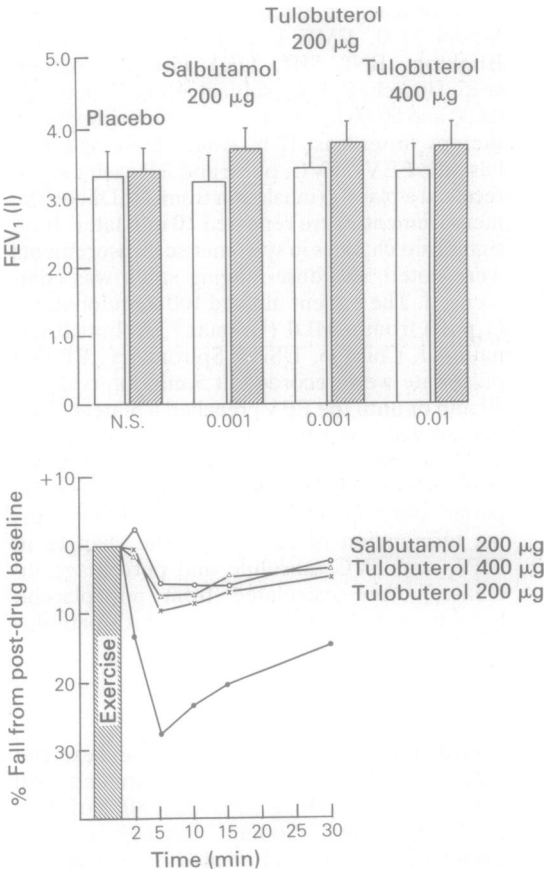

Figure 2 The mean ± s.e. mean ($n = 9$) baseline FEV_1 before (□) and after (▨) treatment on 4 days of exercise testing; and the mean percentage falls in FEV_1 over 30 min after placebo (●), salbutamol 200 μg (○), tulobuterol 200 μg (x) and tulobuterol 400 μg (△).

Discussion

Thirteen of the fifteen patients showed a dose related bronchodilator response to tulobuterol aerosol and the maximal response was observed with a cumulative dose of 600 μg. Eight patients showed an improvement in FEV_1 of greater than 15% by 5 min after inhalation of 100 μg tulobuterol and of these three patients showed a response within 1 min after this dose. In a further nine patients 200 μg and 400 μg tulobuterol inhibited exercise-induced asthma and the inhibitory effect was comparable to 200 μg salbutamol aerosol.

Inhaled β-adrenoceptor agonists are more effective in preventing exercise-induced asthma (Anderson *et al.*, 1975, 1976) compared with β_2-adrenoceptor agonists given orally (Anderson *et al.*, 1976; Francis *et al.*, 1980). Furthermore, the protection offered by β_2-adrenoceptor agonists and the magnitude of bronchodilatation appear to be unrelated (Hetzel *et al.*, 1977). The route of administration of a drug may be an important determinant of its efficacy in blocking exercise asthma. The inhaled route is preferred because of a larger ratio of bronchodilator activity to plasma drug concentrations, rapid onset of action and considerably fewer side effects. Tulobuterol by the inhaled route appears to have a significant bronchodilator response with few side effects.

I thank Mrs R. Jack for technical assistance, Ms J. A. Swanson and Dr E. I. Weis of Abbott International, Chicago, for the supply of drugs and financial support.

References

Anderson, S. D., Rozea, P., Dolton, R & Lindsay, D. A. (1975). Inhaled and oral bronchodilator therapy in exercise-induced asthma. *Aust. N. Z. J. Med,* **5**, 544–550.

Anderson, S. D., Seale, J. P., Rozea, P., Bandler, L., Theobald, G. & Lindsay, D. A. (1976). Inhaled and oral salbutamol in exercise-induced asthma. *Am. Rev. resp. Dis.,* **114**, 493–500.

Francis, P. W. J., Krastins, I. R. B. & Levison, H. (1980). Oral and inhaled salbutamol in prevention of exercise-induced bronchospasm. *Paediatrics,* **66**, 103–108.

Hetzel, M. R., Batten, J. C. & Clark, T. J. H. (1977). Do sympathomimetic amines prevent exercise-induced asthma by bronchodilatation alone? *Br. J. dis. Chest,* **71**, 109–114.

Kubo, S., Kase, Y., Miyata, T., Kito, G. & Uesaka, I. (1975). Pharmacological studies of 1-(o-chlorophenyl)-2-tert-butylamino ethanol (C-78), a new bronchodilator. *Arzneim-Forsch. (Drug Res.,),* **25**, 1028–1037.

Kubo, S., Uesaka, I., Matsubara, I., Ishihara, T. & Kase, Y. (1977). Pharmacological studies of o-chloro-[(tert-butylamino) methyl]-benzylalcohol hydrochloride (C-78), a new bronchodilator II, Actions on cardiovascular systems and smooth muscle organs. *Arzneim-Forsch. (Drug Res.),* **27**, 1433–1439.

Massen, F., Smeets, J. & Polderman, J. (1983). A comparative study of bronchospasmolytic effect of tulobuterol and fenoterol in patients suffering from reversible bronchial obstruction. *Arzneim-Forsch (Drug Res.),* **11**, 1696–1698.

Ogawa, M., Yazawa, T., Tonumu, M., Miwa, K. & Tsukidate, K. (1983). Effect of tulobuterol hydrochloride (Hokunalin) dry powder syrup in infantile bronchial asthma. *Prog. Med.,* **3**, 19.

Patel, K. R. (1981). Calcium antagonists in exercise-asthma. *Br. med. J.,* **282**, 932–933.

Shiota, K. & Kuriharu, N. (1978). Double-blind trial of o-chloro-alpha[(tertbutylamino) methyl] benzyl-alcohol hydrochloride (C-78) in patients with chronic obstructive pulmonary disease. *Jap. J. clin. Med.,* **55**, 868–878.

(Received 30 May 1985, accepted 22 October 1985)