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Nitrendipine therapy in asthmatic subjects

E. M. MULLOY, P. CORMIE, J. HARVEY & J. E. MARLEY[1]
Ham Green Hospital, Pill, Bristol BS20 0HW and Bayer U.K. Ltd, Bayer House, Strawberry Hill, Newbury, Berkshire, RG13 1JA

Nitrendipine was given to eight patients with chronic stable asthma prior to a histamine challenge study and compared in a double-blind cross-over fashion with placebo. There were no significant differences in either the bronchoconstrictor effects of histamine, or in oxygen saturation during the histamine challenges, suggesting that nitrendipine should be safely tolerated if used to treat hypertension in patients with airflow obstruction.

Keywords nitrendipine histamine reactivity asthma

Introduction

Nitrendipine is a new dihydropyridine calcium antagonist with a similar structure and action to nifedipine (Kazda *et al.*, 1983). Calcium antagonists may be useful in the management of hypertension in patients with airflow obstruction since they protect against the bronchoconstrictor effects of exercise, cold air and histamine (Barnes *et al.*, 1981). The effect of nitrendipine on both the bronchoconstrictor and oxygen saturation response to inhaled histamine was studied, since previous work has suggested that nifedipine may decrease arterial oxygen tension during a bronchoconstrictor challenge (Ballister *et al.*, 1986).

Methods

Eight patients with chronic stable asthma were studied. Their mean age was 49 years (range 26–64), mean baseline FEV_1 was 2.0 l s^{-1}, standard deviation (s.d.) 0.8 l s^{-1} whilst taking nitrendipine and 1.9 l s^{-1} s.d. 0.6 l s^{-1} whilst taking placebo.

Mean predicted level of FEV_1 for the group was 3.45 l s^{-1} (range 2.41–4.42). Four were non-smokers, three were ex-smokers and one patient smoked 20 cigarettes per day.

Only two of the patients gave a history of hypertension, one for 2 years and one for 15 years, the first was treated with Navidrex K® and the second with Dyazide® and prazosin. They continued on therapy throughout the study. Seven of the patients were male. All patients required regular inhaled bronchodilators, six were using daily inhaled corticosteroids, one was using bronchodilators only and one oral prednisolone. In addition two were taking a slow release theophylline preparation. All patients studied fulfilled the American Thoracic Society's criteria for the diagnosis of asthma.

The patients were studied in a double-blind cross-over fashion between 2 and 3 h after taking 20 mg of nitrendipine orally, or a matching placebo taken in random order. After baseline measurement of blood pressure and spirometry a histamine challenge test was carried out using the method described by Cockcroft *et al.* (1977). Prior to each challenge test inhaled bronchodilators were withheld for 8 h and theophylline preparations for 24 h. Inhaled steroids were continued unchanged. Measurements were made at the same time of day and the histamine aerosol was generated by the same Wright's nebuliser using 5 ml of the test solution and a flow rate of oxygen at 7 l min^{-1}. Patients wore a nose clip and inhaled the aerosol by tidal breathing through a face mask for 2 min. On the study day subjects recorded bronchodilator usage and peak expiratory flow rates at hourly intervals for the remainder of the day. During the histamine challenge studies oxygen saturation was monitored using a Biox II A (Ohmeda) oximeter with ear probe attachment.

Correspondence: Dr J. Harvey, Ham Green Hospital, Pill, Bristol, BS20 0HW

Statistics

Where data appeared normally distributed, the Student's *t*-test was used in the statistical analyses. Where the data appeared non-normal, the non-parametric Wilcoxon test was used. With a sample size of eight patients, a statistical significance level of 5% and a standard deviation of differences for log PC_{20} and oxygen saturation of 1.0 log mg ml^{-1} and 2.7% respectively, we would be able to detect a difference between treatments of 1.2 log mg ml^{-1} and 3.7% respectively with a power of 80%. Oxygen saturation and log histamine concentration appeared normally distributed. The Student's two-sample test was used to test the treatment (adjusted for period) effect.

Results

The median maximum histamine concentration needed to produce a fall of 20% in FEV_1 (PC_{20}) was 3.0 mg ml^{-1} (interquartile range (IQR) 2.0, 6.0 mg ml^{-1}) for nitrendipine and 1.0 mg ml^{-1} (IQR 0.4, 3.0 mg ml^{-1}) for placebo, this difference was not significant.

With nitrendipine treatment the mean oxygen saturation was 94.1% (s.d. 1.7%) during the histamine challenge, compared with 94.7% (s.d. 1.7%) with placebo. This was also not significant.

Mean blood pressure during the challenge was 124/86 mm Hg when treated with nitrendipine and 126/89 mm Hg when treated with placebo.

Maximum histamine concentration and oxygen saturation at PC_{20} for placebo and nitrendipine are shown in Figure 1.

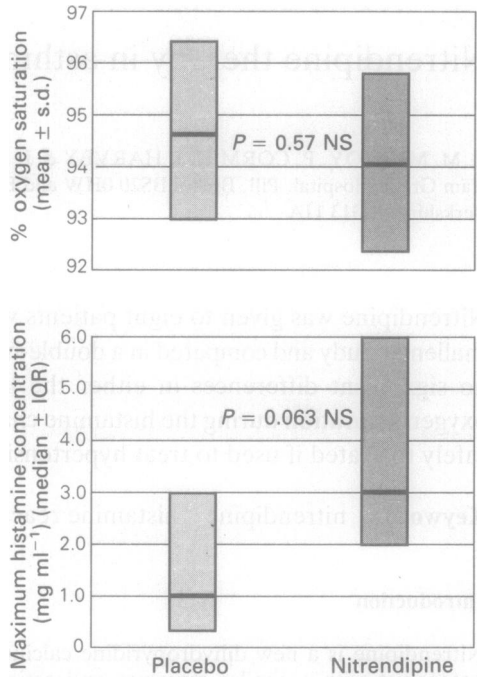

Figure 1 Changes in oxygen saturation and histamine reactivity following treatment with placebo or nitrendipine. IQR interquartile range

Discussion

Nitrendipine is a dihydropyridine calcium antagonist with a similar structure and mechanism of action to nifedipine. Nitrendipine 20 mg daily has been found sufficient to control mild hypertension for 24 h (Andrèn *et al.*, 1982) and is as effective as atenolol 100 mg (De Divitiis *et al.*, 1985). Nitrendipine's advantages over nifedipine may include once daily treatment and improved side-effect profile (Spah & Grosser, 1988). Nifedipine was shown to decrease arterial oxygen tension during a bronchoconstrictor challenge (Ballister *et al.*, 1986). This has not been tested with nitrendipine and as this agent may be used in treating patients with hypertension and obstructive airways disease, for example in preference to β-adrenoceptor blockade, it was important to establish that nitrendipine did not reduce oxygen saturation during the histamine challenge test.

Oxygen saturation was maintained at all histamine concentrations and no significant difference, or trend, was seen in comparison with placebo. The median maximum PC_{20} was higher for nitrendipine, 3.0 mg ml^{-1}, than for placebo, 1.0 mg ml^{-1}. This did not reach significance, but a trend towards protection against bronchoconstriction was seen. No significant difference was seen in blood pressure between treatments, as expected, since nitrendipine does not reduce blood pressure in normotensive subjects (Debbas *et al.*, 1986).

This provoked bronchoconstrictor study in a group of asthmatics with bronchial hyperreactivity suggests that nitrendipine should be well tolerated in patients with coexisting asthma. However, longer term studies of the effect of nitrendipine on bronchial reactivity and airflow obstruction should be performed.

References

Andrèn, L., Hansson, L., Orö, L. & Ryman, T. (1982). Experience with nitrendipine – a new calcium antagonist – in hypertension. *J. cardiovasc. Pharmac.*, **4** (Suppl. 3), S387–S391.

Ballister, E., Roca, J., Rodregeuz-Roisin, R. & Agusti-Vidal, A. (1986). Effect of nifedipine on arterial hypoxaemia occurring after methacholine challenge in asthma. *Thorax*, **41**, 468–472.

Barnes, P. J., Wilson, N. M. & Brown, M. J. (1981). A calcium antagonist, nifedipine, modifies exercise-induced asthma. *Thorax*, **36**, 726–730.

Cockcroft, D. W., Killian, D. N., Mellon, J. J. A. & Hargrave, F. E. (1977). Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin. Allergy*, **7**, 235–243.

Debbas, N. M. G., Jackson, S. H. D. & Turner, P. (1986). A comparison of the haemodynamic effects of nifedipine, nisoldipine and nitrendipine in man. *Eur. J. clin. Pharmac.*, **30**, 393–397.

de Divitiis, O., Petitto, M., Di Somma, S., Galderisi, M., Villari, B., Santomauro, M. & Fazio, S. (1985). Nitrendipine and atenolol: Comparison and combination in the treatment of arterial hypertension. *Arzneimittel Forschung*, **35**(I), 727–729.

Kazda, S., Garthoff, B. & Knorr, A. (1983). Nitrendipine and other calcium entry blockers (calcium antagonists) in hypertension. *Fed. Proc.*, **42**, 196–200.

Spah, F. & Grosser, K. D. (1988). Treatment of hypertensive urgencies and emergencies with nitrendipine, nifedipine, and clonidine: Effect on blood pressure and heart rate. *J. cardiovasc. Pharmac.*, **12** (Suppl. 4), S154–S156.