

Influence of diltiazem on bronchoconstriction induced by cold air breathing during exercise

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ABSTRACT Since the calcium antagonists nifedipine and verapamil have been shown to diminish exercise induced asthma, the effect of oral diltiazem, a calcium channel blocker not previously investigated in this context, was studied. Ten patients with bronchial asthma were given 60 mg diltiazem or placebo four hours before the challenge in a double blind, randomised, crossover fashion. Exercise was performed on a cycle ergometer while the subjects were breathing cold air, resulting in a respiratory heat exchange which was similar at the two study sessions. FEV₁ and specific conductance (sGaw) were recorded before and three, 10, 15, and 30 minutes after the challenge. No significant differences were found between placebo and diltiazem days in the fall of FEV₁ or sGaw after exercise. Thus unlike other calcium antagonists diltiazem, in a dose of 60 mg given orally four hours before exercise, failed to protect against exercise induced asthma.

Exercise induced asthma can be completely or partially inhibited by oral nifedipine¹⁻³ or by inhaled verapamil.⁴ We have investigated another calcium channel blocker, diltiazem, as no study on its ability to influence exercise induced asthma has previously been reported. As respiratory heat exchange is considered to be an initiating stimulus for exercise induced asthma,⁵ the effects of diltiazem and placebo were compared under carefully controlled experimental conditions designed to standardise the inhalation thermal challenge during exercise.

Methods

Patients We investigated 10 patients with bronchial asthma (five men and five women with a mean age of 27.9 years, range 19-41). Nine patients were judged atopic on the basis of positive skin test reactions to common allergens. All patients gave a history suggesting exercise induced asthma. All were non-smokers and did not require regular medication. Sympathomimetic agents, which were taken occasionally, were withheld for 12 hours before the study sessions. The patients were instructed about the aim of the study and gave their consent.

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Cold air breathing during exercise Cold air was produced by passing dried room air through a heat exchanger. Inspiratory and expiratory temperatures were measured by two thermocouples situated within the respective ports of a two way Hans-Rudolf valve (W Collins, United States of America). The water content of both inspired and expired air was calculated from standard saturation-temperature relationships⁶ on the assumption of 100% humidity. Expired air was conducted through a heated pneumotachograph (Fleisch No 4) and airflow was integrated electronically to give tidal volume. Respiratory heat exchange was calculated according to the equation given by Deal *et al.*⁵

Exercise was performed on a cycle ergometer. Following the method of Deal *et al.*,⁵ the patients breathed cold air for four minutes before exercise, while sitting quietly on a cycle ergometer. The duration of exercise was four minutes and this was followed by a further four minutes during which the subjects continued to breathe cold air through the same mouthpiece. For each patient the work load was adjusted to give a minute ventilation of about 50 l min⁻¹, yielding respiratory heat exchange of about 1 kcal (4.184 kJ)/min.

Lung function measurements Thoracic gas volume at functional residual capacity and specific airways conductance during quiet breathing (sGaw) were measured with a constant volume body plethysmograph⁷ (Bodytest, E Jaeger, West Germany). Inspired vital capacity and FEV₁ were measured

after the plethysmographic manoeuvre. At each time interval three plethysmographic and spirometric measurements were made.

Experimental protocol Four hours before the challenge each patient received either placebo or diltiazem, 60 mg, in a double blind, randomised, cross-over fashion. Lung function was assessed before (baseline values) and three, 10, 15, and 30 minutes after the challenges, which were performed on different days at the same time of the day. The work load of the ergometer was constant on both occasions.

Evaluation of data The airway response to exercise during the breathing of cold air was assessed by expressing the lowest values of sGaw or FEV₁ observed after the challenge as percentages of the respective baseline values. The effect of diltiazem in comparison with placebo was quantified in terms of a protection index, given by

$$\frac{\% \text{ fall in sGaw (FEV}_1\text{) after placebo} - \% \text{ fall in sGaw (FEV}_1\text{) after diltiazem}}{\% \text{ fall in sGaw (FEV}_1\text{) after placebo}}$$

The results were analysed statistically with Friedman's test of homogeneity and by the multiple, two tailed comparison of Wilcoxon and Wilcox.⁸

Results

The pre-exercise values of airway function and the ventilation and respiratory heat exchange on exercise after pretreatment with placebo and diltiazem are compared in figure 1. In all patients sGaw and FEV₁ were normal before the challenge. There were no significant differences between prechallenge lung function data, exercise ventilation, inspired air temperature, or respiratory heat exchange on the two days.

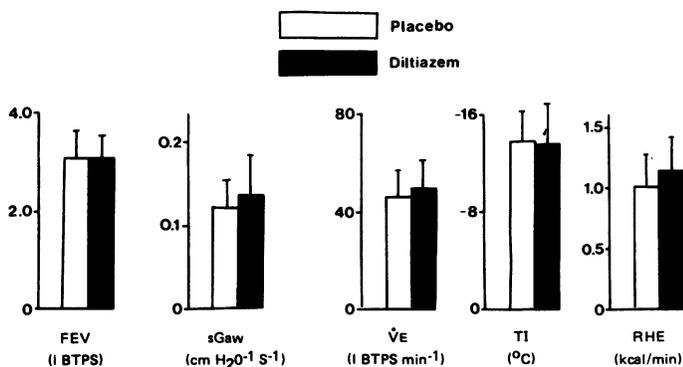


Fig 1 Comparison of the experimental conditions after pretreatment with placebo and diltiazem. FEV₁ and sGaw were determined before challenge (baseline values). VE—minute ventilation during exercise; TI—inspiratory air temperature; RHE—respiratory heat exchange. Statistical comparison showed no differences between the results for placebo and diltiazem. Conversion: Traditional to SI units—heat exchange: 1 kcal = 4.184 kJ.

The course of the airway response was similar for sGaw and FEV₁ after pretreatment with placebo and diltiazem and is shown in terms of sGaw for each patient in figure 2. It can be seen that the response to the challenge varied considerably between the patients. Apart from patient 1, pretreatment with diltiazem did not change the pattern of response. For the group as a whole there were no significant differences between the maximum bronchoconstriction or airway function at any specific time after the challenge on placebo and diltiazem days. With placebo and diltiazem pretreatment the mean (SD) maximum percentage falls of FEV₁ were 24.8 (20.1) and 21.7 (17.5). The mean (SD) maximum percentage decreases of sGaw were 66.2 (18.4) and 62.7 (23.9) respectively. The protection index calculated for each lung function measurement did not differ statistically from zero.

Discussion

In patients with exercise induced asthma diltiazem, 60 mg, taken orally four hours before exercising while they breathed cold air, did not alter the bronchoconstriction response when compared with placebo. This result clearly contrasts with the protective effect of nifedipine on exercise induced¹⁻³ and hyperventilation induced^{9,10} asthma and with the ability of inhaled verapamil to blunt exercise induced airway obstruction.⁴ Three factors that could be responsible for this discrepancy must be considered—namely, the methodological, pharmacokinetic, and pharmacological aspects.

In our group of patients cold air breathing during exercise resulted in a respiratory heat exchange which was not different on the two days. As in some patients small differences in respiratory heat exchange after pretreatment with placebo and diltiazem could not be avoided, we re-evaluated the data by relating the results to the respiratory heat

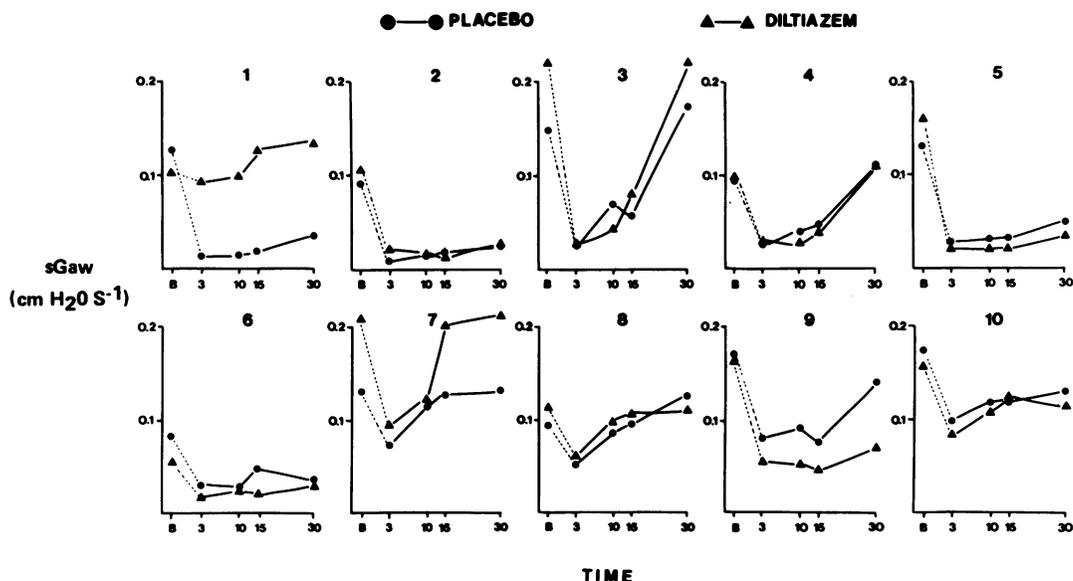


Fig 2 Time course of specific airway conductance ($sGaw$) after pretreatment with placebo and with diltiazem, shown for patients 1-10. B—baseline value; 3, 10, 15, 30—time (in minutes) at which lung function was measured after challenge.

exchange actually measured during the study; but this again failed to show a difference between placebo and diltiazem.

Diltiazem was given as a single dose before the challenge in the same way as in the study in which the inhibitory effect of nifedipine on exercise induced asthma was most clearly documented.¹ The dose used is that recommended for a single oral application of diltiazem. The choice of an interval of four hours between ingestion of the capsule and the challenge is based on pharmacokinetic data showing a peak serum concentration of diltiazem between the second and fourth hour after ingestion.¹¹ We therefore think it unlikely that pharmacokinetic factors are responsible for the different results.

The lack of effect of 60 mg diltiazem compared with 20 mg nifedipine could be explained simply by a relative underdosage of diltiazem. In our laboratory, however, we have shown that a 60 mg dose of diltiazem taken orally four hours before an inhalation challenge protected against histamine and carbachol induced bronchoconstriction in patients with hyperreactive airways. After diltiazem the cumulative breath units of histamine and carbachol causing a fall in $sGaw$ of 35% were approximately doubled (unpublished observations). As nifedipine attenuates histamine induced^{12,13} and allergen induced¹⁴ bronchoconstriction in man and diminishes airway obstruction after antigen and methacholine inhala-

tion in the dog¹⁵ the ineffectiveness of diltiazem compared with nifedipine is unlikely to be simply a question of dosage. Russi *et al*¹⁶ recently showed in allergic sheep that verapamil prevented bronchoconstriction induced by allergen but did not modify the airway response to histamine and carbachol challenge. These results show that the effects of different calcium channel blockers in protecting against bronchoconstriction vary with the stimuli, but further studies are required to elicit the mechanisms of their actions.

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