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Nifedipine enhances the bronchodilator effect of salbutamol

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ABSTRACT Ten male asthmatic volunteers each inhaled two puffs (200 μg) of salbutamol on two separate days 30 minutes after double blind oral administration of either 20 mg nifedipine or identical placebo. FEV_1 was recorded before and at intervals for four hours after inhalation of salbutamol. Overall the FEV_1 was significantly greater during the four hour period after premedication with nifedipine ($p < 0.025$) and the difference between the effects of placebo and nifedipine was greatest four hours after salbutamol ($p < 0.005$). These results suggest that nifedipine prolongs the bronchodilator action of salbutamol in vivo.

Nifedipine is a dihydropyridine derivative which inhibits transmembrane flux of calcium ions, and several studies have shown that it may attenuate asthma induced by exercise or by histamine.[1-4] Another calcium antagonist, verapamil, has been shown to enhance both the degree and the duration of smooth muscle relaxation induced by various bronchodilators in the guinea pig trachea in vitro.[5] We have therefore investigated the effect of nifedipine on the acute bronchodilator action of salbutamol in a group of asthmatic subjects.

Methods

Ten male volunteers with stable asthma were studied (table). Six were atopic and none smoked. The subjects were chosen so that the best recorded FEV_1 of each was no more than 75% of the predicted normal value. At the time of study their FEV_1 values ranged from 33% to 60% predicted (table). None was taking sodium cromoglycate, oral corticosteroids, or theophylline and no inhaled bronchodilators or steroids were taken within 12 hours of the study. Each subject attended at the same time in the morning on two days; two puffs (200 μg) of salbutamol were inhaled 30 minutes after premedication with either nifedipine (two 10 mg capsules) or identical placebo given orally in randomised double blind fashion. The subjects were instructed to bite the capsules, keeping the liquid in the mouth for as long as possible before swallowing it. Baseline FEV_1 recordings were taken before premedication and the FEV_1 at the second attendance had to be within ±15% of the first, otherwise the study was deferred until another day. Measurement of FEV_1 was repeated 30 minutes after they had taken the capsules (that is, immediately before inhalation of salbutamol) and 15, 30, and 45 minutes and one, two, and four hours after inhalation. The changes in FEV_1 from the baseline measurement (ΔFEV_1) at each time interval, as well as the maximum ΔFEV_1, on placebo and nifedipine days were compared by means of paired t tests. The overall effect of nifedipine was also assessed by comparing the areas under the curves of ΔFEV_1 plotted against time on the two study days.

Results

One subject complained of flushing and headache after taking the active preparation but no other unwanted effects were noted. There were no significant differences between baseline FEV_1 values before placebo or nifedipine, and although the mean increase in FEV_1 30 minutes after ingestion of nifedipine was greater than after placebo the difference was not statistically significant. The maximum ΔFEV_1 was slightly but not significantly greater on nifedipine days than on placebo days (table). The ΔFEV_1 at each time interval was also greater on nifedipine days (fig) but the difference was only significant at 4 hours (that is, 4½ hours after nifedipine—table). The areas under the curves on

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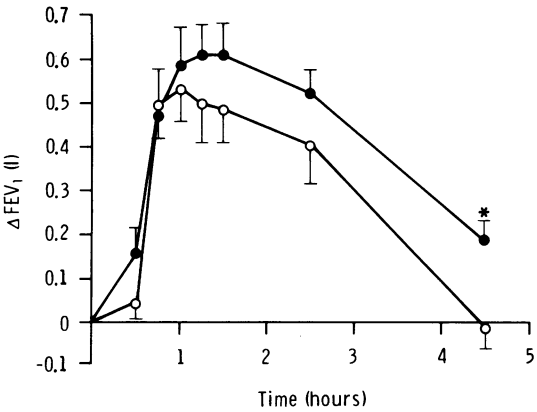
Details of patients and changes in FEV_1

Subject No	*Age (y)*	*Atopic +/−*	*Baseline FEV_1**		*Maximum ΔFEV_1 (l)*		*ΔFEV_1 (l) 4 h after salbutamol*	
			(l)	*(% predicted)*	*Placebo*	*Nifedipine*	*Placebo*	*Nifedipine*
1	33	+	1·9	51	0·85	0·75	−0·15	0·3
2	54	−	0·9	33	0·4	0·9	0·2	0·3
3	50	+	1·15	45	0·35	0·8	−0·15	0·2
4	55	+	1·75	50	0·55	0·6	0·3	0·35
5	60	−	1·1	36	0·75	0·7	−0·05	0·2
6	50	−	1·6	54	0·6	0·65	0·15	0·15
7	58	+	1·7	48	0·4	0·6	−0·1	0·3
8	46	+	1·25	34	1·0	1·2	0	0·1
9	47	−	2·3	60	0·5	0·35	−0·05	0
10	32	+	1·7	43	0·3	0·4	−0·25	0·1
Mean	48·5		1·53	45·4	0·57	0·70	−0·015	0·18
SD	9·5		0·43	9·0	0·23	0·24	0·17	0·14
p					N.S.		0·005	

*Mean of two study days.
NS—not significant.



*Changes in FEV_1 (ΔFEV_1) plotted against time after premedication with either placebo (○) or nifedipine (●): 200 μg salbutamol was inhaled at 30 minutes. Bars represent standard errors. *$p < 0·005$.*

nifedipine days were significantly greater than on placebo days (mean 1825 (SD 671) and 1260 (819) arbitrary units respectively; $p < 0·025$).

Discussion

Smooth muscle cells contract after a rise in cytoplasmic free calcium ions. Beta adrenergic stimulants such as salbutamol are thought to produce relaxation of smooth muscle by raising the level of intracellular cyclic AMP, which reduces cytoplasmic free calcium ions by binding calcium ions to the cell membrane and cytoplasmic reticulum. Nifedipine inhibits entry of calcium ions into smooth muscle cells by blocking potential dependent calcium channels.[6] Thus the addition of a calcium antagonist to a β stimulant might be expected to increase its effect.

The results of the present study suggest that nifedipine attenuates the effect of various bronchoconstricting stimuli in asthmatic subjects,[1-4] just as it enhances and prolongs the action of a bronchodilator, but the effect was small with the dose used. The potential benefit was more evident in prolonging the action of salbutamol than in producing a greater peak effect and this is similar to the effect of increasing the dose of β stimulant.[7] There was considerable variability between individuals in the effect of nifedipine, but no specific features were recognised which distinguished subjects in whom a larger or smaller effect was seen.

Although no acute bronchodilatation has been demonstrated after administration of nifedipine in this or any previous study, a small effect is not excluded. The effect is detectable in the presence of a conventional bronchodilator drug and the smooth muscle relaxation induced by the combination suggests a possible clinical role for calcium antagonists in asthma, which merits further study.

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