

Nifedipine – a Calcium Channel Blocker – in Asthmatic Patients

Interaction with Terbutaline

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Seven asthmatic patients were studied in a single-blind randomized, crossover study after oral administration of 20 mg nifedipine or placebo. Four increasing doses of i.v. terbutaline were then given with 30 min interval. The study was concluded with inhalation of five terbutaline puffs. FEV₁ measurements 30 min after intake of nifedipine did not show any difference compared to placebo. During the terbutaline treatment, however, there was a more pronounced bronchodilation after nifedipine than after placebo ($P < 0.05$). Terbutaline-induced skeletal muscle tremor was similar after nifedipine and placebo pretreatments. After nifedipine intake there was a decrease of diastolic blood pressure and a reflexogenic tachycardia. Thus, this study showed a small potentiation of the β_2 -adrenoceptor mediated bronchodilation, which is of importance when treating patients with simultaneous asthma and hypertension or angina pectoris.

Key words: calcium channel blocking agent; terbutaline; dose-response effect; hemodynamic effects; skeletal muscle tremor; potentiation.

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The central role of the calcium ion in the contraction of smooth muscle is well established (10). It is also known that cyclic AMP can activate protein kinases which bind intracellular calcium ions and result in smooth muscle relaxation (2).

Thus, it seems theoretically possible that calcium antagonists have a direct effect on bronchial smooth muscle, as they decrease intracellular calcium levels (9), and also that the lower intracellular calcium concentration after calcium antagonists could potentiate the action of a β_2 -adrenoceptor agonist. This effect has been described in isolated guinea pig tracheal tissue (13).

The use of calcium antagonists in clinical medicine has increased in recent years, and they have been used partly on the same indications as β -adrenoceptor antagonists (3, 6). As β -adrenoceptor antagonists can give broncho-

constriction in asthmatic patients (15), it is clinically important to find alternative treatment regimens for asthmatic patients with angina pectoris, hypertension and cardiac arrhythmias. Therefore, it was interesting to study the effect of nifedipine, a calcium channel antagonist in asthmatic patients, in order 1) to evaluate whether a bronchodilating action could be found and 2) to study the possibility of a potentiation of the β_2 -adrenoceptor agonist answer.

METHODS

Experimental design

The study was performed as a single-blind, randomized, crossover comparison in stable intrinsic asthmatics in which placebo and nifedipine, 20 mg, was given orally. This was followed by an intravenous terbutaline dose-response

experiment where four doses were given. The experiment was concluded each time by inhalation of terbutaline from a metered aerosol. To avoid carry-over effects there was at least 2 days' interval between each test day.

The design of the study was approved by the Ethical Committee of the University of Gothenburg.

Patients

Seven patients with intrinsic asthma were included in the study. Details of the patients are given in Table 1. All patients had previously proved to have a reproducible airways obstruction, when off treatment, with a reversibility of 20–50% of the five inhalations of terbutaline sulphate (1.25 mg). Four patients were cigarette smokers. If the difference in basal values of FEV_1 between examination days was greater than 20%, the experiment was repeated. The study was performed in a stable phase without any signs of exacerbation.

Table 1 shows previous drug treatment. Before the study β_2 -adrenoceptor stimulants were withdrawn 11 h before each experiment. Theophylline therapy was stopped 36 h before the

trial. Patients on steroids continued the therapy during the study.

Experimental details

The patients arrived at the laboratory at 7.30 a.m. after having eaten a light breakfast without coffee or tea. An intravenous catheter was inserted in a superficial arm vein. The patient then rested comfortably in a semi-recumbent position for 60 min, after which basal measurements were made. Patients were seated in a semi-recumbent position throughout, and the following measurements were made in the following order:

- 1) Heart rate from a continuous ECG recording.
- 2) Blood pressure by the cuff method.
- 3) Skeletal muscle tremor with a single plane accelerometer according to the earlier described method. The tremor was expressed as tremor ratio, where recorded values after treatment were divided by the basal value in each patient. Patients on regular β_2 -stimulants experienced tremor at a mean tremor ratio of about 1.7 (19).

Table 1
Clinical details of patients

Patients	Sex	Age	Weight (kg)	Length (cm)	Diagnosis	Duration of asthma (years)	Smoking history	FEV_1 before study 1	Treatment
KJ	M	31	74	173	A	5	10–15 cig/day	2.25	Bec, OBR, IBR
HE	M	53	102	173	A + C	12	12 cig/day	1.25	OBR, IBR
LL	M	49	91	176	A + C	11	–	2.45	OBR, IBR
EZ	M	48	70	175	A	5	3–4 cig/day	1.35	OBR, IBR
AM	F	42	46	157	A + C	2	–	1.45	Bec, IAR, OBR, IBR
TN	M	66	69	178	A + C	32	12 cig/day	1.30	OBR, IBOD
AJ	M	57	86	177	A	7	–	1.70	Bec, OBR, IBR, D

Bec = beclomethasone dipropionate by inhalation.

OBR = oral β -stimulants regularly (salbutamol or terbutaline).

IBR = inhaled β -stimulants regularly (salbutamol or terbutaline).

IAR = inhaled anticholinergics regularly (ipratropium bromide).

IBOD = inhaled β -stimulants on demand (salbutamol or terbutaline).

D = disodium chromoglycate by inhalation.

A = asthma.

C = chronic bronchitis.

- 4) Forced expiratory volume in 1 sec (FEV_1) was measured with a Bernstein spirometer. Two recordings were made, and the highest used for calculation.

After basal measurements, placebo or 20 mg nifedipine (Adalat®, Bayer) was given in capsules. 30 min after oral intake all measurements were repeated, and then followed by the first of four terbutaline infusions given with an infusion pump. The infusion duration was 6 min and the interval between the terbutaline infusions was 30 min. The doses given were 0.024, 0.078, and 0.58 and 0.82 $\mu\text{g kg}^{-1} \text{min}^{-1}$. All measurements were repeated 7–10 min after the start of each infusion. 15 min after the last terbutaline infusion the patient inhaled five puffs of terbutaline from a metered aerosol (Bricanyl®, Draco, 1.25 mg) and 5 and 15 min later all measurements were repeated.

Statistical methods

The results are shown as mean values $\pm$ standard errors of the mean (SEM). Significant differences between the different treatments were tested by Student's paired t-test. Assessment of statistical significance was based on the conventional levels ($P < 0.05$, $P < 0.01$ and $P < 0.001$). The estimation of difference during the terbutaline dose-response experiments was based on the mean individual values of the effect from four doses, thereby decreasing the measurement variation (15). The estimation of difference after terbutaline inhalation was based on the mean individual value of the effect measured 5 and 15 min after inhalation.

RESULTS

Respiratory studies

Effect on FEV_1 is shown in Fig. 1. After 30 min there was no significant difference between nifedipine and placebo (0.07 ± 0.04 l). During the terbutaline dose-response experiment there was a dose-dependent increase in FEV_1 after both placebo and nifedipine treatment. The mean difference after the four i.v. terbutaline

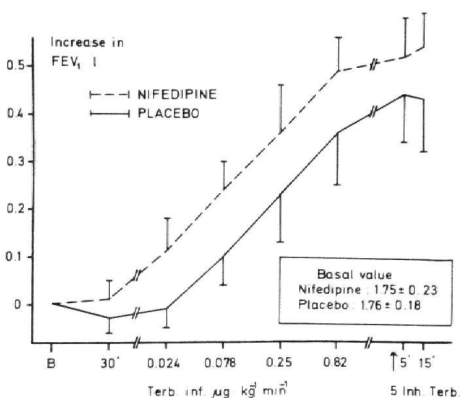


Fig. 1. Mean change FEV_1 ($\pm$ SEM, only one direction in the graph). 30 min after intake of 20 mg nifedipine or placebo, after four increasing doses of i.v. terbutaline and 5 and 15 min after inhalation of 1.25 mg terbutaline.

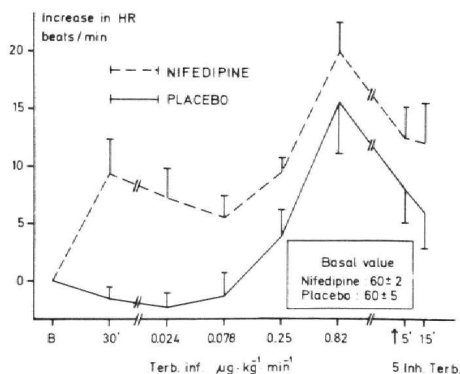


Fig. 2. Mean change of heart rate ($\pm$ SEM, only one direction in the graph). 30 min after intake of 20 mg nifedipine or placebo, after four increasing doses of i.v. terbutaline and 5 and 15 min after inhalation of 1.25 mg terbutaline.

doses between nifedipine and placebo pre-treatments was 0.14 ± 0.05 l ($P < 0.05$). After inhalation of terbutaline the mean difference between nifedipine and placebo treatments was 0.10 ± 0.04 l (n.s.).

Cardiovascular studies

Heart rate: Fig. 2 shows that after nifedipine treatment there was an increase of heart rate, 9 ± 3 beats/min. The difference between nifedi-

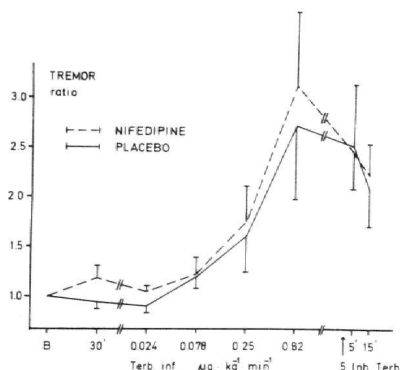


Fig. 3. Mean change of tremor ratio ($\pm$ SEM, only one direction in the graph). 30 min after intake of 20 mg nifedipine or placebo, after four increasing doses of i.v. terbutaline and 5 and 15 min after inhalation of 1.25 mg terbutaline.

pine and placebo was 11 ± 4 ($P < 0.05$). During terbutaline infusions all values after nifedipine treatment tended to be higher than after placebo treatment. However, the differences were not significant.

The variation in systolic blood pressure did not make it possible to find any significant changes between different treatments. Diastolic blood pressure, 30 min after oral intake, showed significant decrease after nifedipine intake. The difference between nifedipine and placebo pretreatment was 8 ± 2 mmHg ($P < 0.05$).

Skeletal muscle tremor studies

Significant differences in the different treatments between either placebo or nifedipine, were not shown (Fig. 3).

DISCUSSION

These studies showed that neither 20 mg nifedipine or placebo produced any significant bronchodilation in asthmatics. However, during terbutaline infusion there was a significantly better bronchodilation after nifedipine pretreatment.

As calcium channel blockers decrease transmembrane penetration of calcium, calcium de-

pendent activities in the cells are reduced. This has been shown in cardiac cells and in different smooth muscle cells (1, 5, 16, 18). In isolated tracheal tissue from guinea pig, nifedipine has been shown to decrease the effect of bronchoconstrictive drugs (7). However, there was a difference between histamine- and carbacholine-mediated bronchoconstriction. The effect of nifedipine could be diminished by an increased extracellular calcium ion concentration, supporting the idea that nifedipine acts by a calcium-mediated effect. Other calcium channel blockers have given similar *in vitro* results (12, 13).

Animal *in vivo* experiments have shown an attenuation of histamine-induced bronchoconstriction in guinea pig (7). In dog experiments nifedipine and verapamil were shown to have a weak bronchorelaxing effect. The effect on resting bronchial tone was much weaker than the effect on blood flow in the trachea (11).

Nifedipine (4, 20) and verapamil (17) have been shown to have no effect on resting bronchial tone in asthmatic patients. Also the present study failed to show any effect on resting bronchial tone.

However, an effect of calcium antagonists on airway reactivity has been shown in exercise-induced asthma. Patel (17) showed decreased post-exercise bronchoconstriction after verapamil treatment. The effect was similar to that of sodium cromoglycate. Cerrina et al. (4) showed that nifedipine had a preventive effect on exercise-induced asthma and totally abolished the post-exercise bronchoconstriction. Williams et al. (20) have shown decreased histamine reactivity in asthmatics. Thus, calcium channel blockers have been shown to affect the regulation of bronchial tone both *in vitro* and *in vivo*.

The interaction with a β_2 -adrenoceptor stimulant has not yet been studied in asthmatic patients. Experimental studies have proposed that calcium channel blockers of bronchodilating drugs have a potentiating effect (13). The present study showed a small potentiating effect in asthmatic patients of nifedipine on the β_2 -adrenoceptor-mediated bronchorelaxation, but no effect on the resting bronchial tone.

The statistical analysis of these data was done according to earlier described methods (15).

Nifedipine gave a peripheral vasodilation which induced a reflex tachycardia. A possibility which has to be considered is that sympathetic stimulation via adrenal hormones might induce bronchodilation. However, the absence of effect on FEV₁ 30 min after tablet intake speaks against this explanation.

The effect on skeletal muscle tremor is interesting from the clinical point of view, as tremor is the main side effect of β -adrenoceptor agonist (14). The present study did not show any increase of tremor with nifedipine. This might seem surprising as Ca-ions are involved in the contractile mechanism of skeletal muscle (10). However, the intra-cellular concentration of calcium in skeletal muscle is so high that a calcium channel blocker does not influence the contractile mechanism (8).

There is another important clinical implication of the finding of potentiation of β -adrenoceptor by a calcium channel blocker, as the indications for calcium channel blockers are much the same as those for β -adrenoceptor antagonists. The latter are known to be hazardous to asthma patients even if an increased β_1 -adrenoceptor selectivity decreases this risk (15). Therefore, the first choice in asthmatic patients with angina pectoris, hypertension and cardiac arrhythmias seems to be calcium channel blockers, and a second choice, if necessary, a highly selective β_1 -adrenoceptor antagonist.

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