Efficacy of calcium channel blockers as maintenance therapy for asthma

Mary Ann Twiss,^{3*†} Eloise Harman,¹ Sarah Chesrown² & Leslie Hendeles^{2,3}

³The Department of Pharmacy Practice, College of Pharmacy, ¹the Division of Pulmonary/Critical Care Medicine, Department of Medicine and

²the Paediatric Pulmonary Division, Department of Paediatrics, College of Medicine, at the University of Florida, Gainesville, Florida, USA

Aims Previous bronchoprovocation studies indicate that nifedipine attenuates airway responsiveness to several stimuli whereas diltiazem has no effect. The aim of this study was to determine whether such studies predict the efficacy of calcium channel blockers as maintenance therapy for persistent asthma.

Methods Twenty-one otherwise healthy adults with persistent asthma, mean age 25 years, completed treatment with maximum tolerated doses of placebo (P), nifedipine (N), and diltiazem (D) in a double-blind, randomized, three-treatment, three-period, crossover manner, each for 4 weeks. Frequency and severity of asthmatic symptoms were recorded twice daily, as well as peak expiratory flow and frequency of 'prn' use of inhaled terbutaline. Blood pressure, heart rate, P-R interval of the ECG and spirometry were measured biweekly. At the end of each treatment, airway responsiveness to exercise was measured.

Results The mean (s.e. mean)% of days with wheeze was $69 \pm 7\%$ during P, $75 \pm 6\%$ during N and $72 \pm 6\%$ during D ($P=0.7$). FEV₁ was $79 \pm 2\%$ of predicted during P, $81 \pm 2\%$ during N and $79 \pm 2\%$ during D ($P=0.6$). The decrease in FEV₁ after exercise was $32 \pm 4\%$ during P, $32 \pm 5\%$ during N and $27 \pm 4\%$ during D ($P=0.5$). Heart rate was elevated during N ($P=0.0002$) whereas P-R interval was prolonged during D ($P=0.0001$).

Conclusions Maintenance therapy with calcium channel blockers, at doses that produce cardiovascular effects, do not suppress the signs and symptoms of persistent asthma. Previous bronchoprovocation studies did not predict these results.

Keywords: diltiazem, nifedipine, calcium channel blockers, asthma

Correspondence: Leslie Hendeles, Pharm.D., University of Florida (Box 100486), Gainesville, FL 32610-0486, USA. Tel.: 1-352-392-5677; Fax: 1-352-846-2498; E-mail: hendeles@cop.ufl.edu

*This work was completed while Dr Twiss was a Clinical Pharmacy Fellow in the College of Pharmacy, University of Florida.

†Present address: Director, Clinical Operations, Quintiles, Kansas City, MO, USA.

Initial statistical analysis of the data was performed as detailed in **Methods**. It is usually a stipulation of the Journal that 95% confidence intervals of the difference between treatment effects are required and this further analysis was requested of the authors during the review process. Regrettably some of the original data were mislaid after the initial analysis and so calculation of the confidence intervals proved impossible. The paper is published in its current format acknowledging these exceptional circumstances.

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Introduction

Altered regulation of transmembrane and intracellular calcium concentrations in mast cells and airway smooth muscle may play a role in the pathogenesis of asthma [1–3]. Many studies have documented that single doses of calcium channel blockers attenuate airway responsiveness to exercise [4–6], and cold air [7, 8] in subjects with asthma. In contrast, there are conflicting results for attenuation of airway responsiveness to methacholine [6, 9, 10], histamine [9, 11], and allergen [12, 13]. In one study, graded doses of nebulized diltiazem had no effect on airway responsiveness to exercise or methacholine [14], whereas a similar study design indicated that inhaled gallopamil (methoxyverapamil) attenuated both [6]. Nifedipine may have a bronchodilator effect [15–17], as well as enhancing the bronchodilator effects of

β_2 -adrenoceptor selective agonists [18, 19]. Thus, it appears that the efficacy of calcium channel blockers in preventing experimentally induced bronchospasm is a function of the drug, dose, and route of administration.

The results of previous studies of the benefit of maintenance therapy with calcium channel blockers for persistent asthma have been equivocal [17, 20–24]. However, it is unclear whether the negative results were a function of study design or an inherent lack of efficacy of this group of drugs. Potential benefit may have been missed due to low doses, small sample size, short observation periods, inclusion of subjects with COPD or a combination of these factors.

The present study was undertaken to determine if maximum tolerated doses of oral nifedipine and diltiazem, each administered for a 4 week period in a double-blind placebo-controlled trial could suppress the signs and symptoms of persistent asthma. It was our hypothesis that the results of bronchoprovocation studies could be used to predict which calcium channel blocker would be clinically effective as maintenance therapy. Nifedipine was selected because it consistently demonstrated efficacy in bronchoprovocation studies [4, 5, 7, 11, 25–27] while diltiazem was consistently ineffective [10, 14, 28].

Methods

Subject selection

Thirty otherwise healthy adults with persistent asthma, mean age 25 years, were selected from a cohort of subjects who had participated in other studies in our laboratory. All had a documented history of symptoms of asthma at least 50% of days/month, and regular or frequent use of bronchodilators. The diagnosis of asthma was previously confirmed in subjects with an $FEV_1 \geq 65\%$ by methacholine or exercise challenge or responsiveness to inhaled salbutamol in those with an $FEV_1 < 65\%$ predicted. Subjects were excluded if in the previous 90 days they required oral corticosteroids, were treated in an emergency department or were hospitalized for asthma, or if in the previous 30 days they had symptoms of an upper respiratory tract infection. None of the subjects used other antiasthma or antiallergic medication. The study was approved by the University of Florida Health Center Institutional Review Board, and witnessed written informed consent was obtained from each subject.

Dosage titration

Subjects first underwent determination of the maximum tolerated oral dose of nifedipine and diltiazem in an open trial. During this time, they were instructed in the technique of measuring peak expiratory flow (PEF) with

an Assess Flowmeter (Healthscan Products, Inc., Upper Montclair, NJ), and were acquainted with the subject diary form in which symptom scores, PEF and all medication use were to be recorded during the study. Diltiazem was started at 120 mg day⁻¹ in four divided doses, and increased by 120 mg every 72 h as tolerated. Nifedipine was started at 40 mg day⁻¹ in four divided doses and increased by 40 mg every 72 h, as tolerated. The maximum tolerated dose was defined as the highest dose that did not cause subjective side-effects or result in >15% change in blood pressure, heart rate or P-R interval of the electrocardiogram. The maximum tolerated dose determined during the open trial was then administered during the double-blind study (Table 1).

Study design

This was a double-blind, randomized, three-period, three-treatment, crossover trial during which subjects received diltiazem/placebo, nifedipine/placebo and placebo/placebo, each for 4 weeks. There was no washout period between treatments but data for the first week of each treatment was excluded from analysis to decrease the likelihood of a carryover effect. Regular use of bronchodilators was discontinued in all subjects for the duration of the study. Asthmatic symptoms were managed with as needed ('prn') inhaled terbutaline by metered dose inhaled (Brethaire, Ciba-Geigy Corp.). The terbutaline canisters were attached to an electronic monitor, the Nebulizer Chronolog (Advanced Technology Products, Denver, CO), which stored the date, time and number of puffs actuated [29]. Subjects were instructed to contact the study nurse if inhaler use exceeded 8 puffs per day or if symptoms of asthma became unresponsive to terbutaline. Subjects with bronchodilator unresponsive symptoms then received a course of oral prednisone at a dose of 40 mg twice daily until symptom free for 24 h up to a maximum of 7 days, without tapering. If prednisone was required for more than 7 days or a second course was required during any treatment regimen, the regimen was considered a failure, and the subject was assigned to the next treatment.

Response to treatment was assessed by: (1) symptom scores from daily diaries on a 0–3 scale where 0 indicated the absence of symptoms and 3 indicated that the symptoms were severe and interfered with sleep or daytime activities; (2) PEF measured twice daily; (3) use of additional medication; (4) spirometry expressed as a percent predicted [30], electrocardiogram and blood pressure, measured biweekly; and (5) maximum percentage decrease in FEV_1 after a standardized exercise challenge performed at the end of each 4 week period.

Adherence to study medication was determined by diary review and pill counts at each visit. Accuracy of diary

Table 1 Demographic data and results of screening procedures for the 24 subjects who completed the study.*

Subject	Age (years)	Gender	FEV ₁ (% predicted)	Maximum tolerated dose (mg day ⁻¹)	
				Diltiazem	Nifedipine
01	26	M	47	360	160
03	23	F	100	360	80
04	21	F	96	360	40
05	24	F	89	360	120
06	20	F	84	360	80
07	38	M	52	240	80
08	24	F	60	360	80
09	25	M	68	360	80
10	23	M	75	480	120
11	23	M	71	360	80
12	22	M	47	480	80
13	19	F	94	480	120
14	32	M	60	360	80
15	35	M	98	480	120
16	24	M	78	480	120
17	20	F	60	480	120
18	22	F	66	480	40
20	26	M	71	240	40
21	18	M	63	360	80
23	22	F	91	360	40
24	24	M	82	360	40
25	23	M	91	480	80
27	24	F	68	360	160
30	24	F	100	360	40
Mean	24	13M/11F	75	390	87
s.e. mean	1		3	15	7

*Three of the subjects were excluded from final data analysis because of packaging errors in the blinded treatments.

recordings also was determined by comparing the subject's recorded values for inhaled terbutaline use with the download from the Nebulizer Chronolog computerized record.

Pfizer Laboratories (New York, NY) provided nifedipine and matching image placebo while Marion Laboratories (Kansas City, MO) provided diltiazem and matching image placebo. The Investigational Drug Unit of the Pharmacy Department at the Shands Hospital of the University of Florida prepared the blinded medication according to a computer generated randomization schedule and the calcium channel blocker dose determined during the titration period.

Exercise challenge

A standardized treadmill exercise challenge for asthma [31] was performed at the completion of each 4 week treatment, 2 h after the last morning dose of study drug. Treadmill workload was standardized by altering the incline and speed over 3–4 min to achieve target conditions of a minute ventilation of 55% to 65% of calculated maximum voluntary ventilation based on the subjects measured FEV₁ [32]. Minute ventilation was

included to guide treadmill speed and incline since calcium channel blockers can affect heart rate. If heart rate alone would have been used, subjects would have received unequal workloads between treatment regimens. Minute ventilation and oxygen consumption were measured in a breath-by-breath fashion by a Beckman Metabolic Measurement Cart (Beckman Instruments, Anaheim, CA). During exercise, subjects breathed ambient air maintained between 22°C and 24°C and 40% to 50% relative humidity. They were exercised at the same target conditions, for minute ventilation and oxygen consumption, for 6 min Spirometry was performed before and at 3, 5, 8, 10, and 15 min after exercise.

Data analysis

Symptom scores were tabulated from the diaries and expressed as the percent of days that each symptom was present on each treatment regimen. The analysis of variance for repeated measures was used to determine the statistical significance of mean differences between diltiazem, nifedipine and placebo for each symptom score, frequency of inhaler use (based on Chronolog data), PEF, biweekly spirometric and cardiovascular

measurements, oxygen consumption, minute ventilation and heart rate during the exercise stress test and the decrease in FEV₁ after exercise. The Ryan-Einot-Gabriel-Welsch multiple *F*-test was used to determine the source of a difference when ANOVA was significant. The Chi-square analysis was used to compare the frequency of side-effects and need for rescue therapy with prednisone during each treatment. All results are expressed as the mean $\pm$ s.e. mean unless otherwise indicated.

Results

Six subjects were discontinued from the study for the following reasons: need for prednisone during the titration period (two subjects), poor adherence (three subjects), and one subject moved away. Data from three additional subjects who completed the study were excluded when it was discovered that a packaging error resulted in these subjects receiving two courses of the same regimen rather than three different regimens. Therefore, of the 30 subjects who entered the study, data from 21 were analysed.

All treatments were generally well-tolerated. No subject discontinued the study because of an adverse event, although minor side-effects were reported on the nifedipine regimen including dizziness, headache, nausea and abdominal bloating.

There was no significant difference between placebo, nifedipine, or diltiazem treatments for percent of days symptomatic with regard to nocturnal awakenings, intolerance to daytime activity, wheezing or coughing

(Figure 1). Stated another way, subjects were completely symptom-free only $16 \pm 4\%$ of days during placebo, $19 \pm 5\%$ during nifedipine and $20 \pm 5\%$ during diltiazem ($P=0.9$). Also, there was no significant difference between regimens in morning and evening PEF (Figure 2). The average number of puffs/day of terbutaline metered-dose inhaler required for relief of symptoms was 3.9 ± 0.6 puffs/day during placebo, 3.7 ± 0.7 puffs/day during nifedipine and 3.5 ± 0.6 puffs/day during diltiazem ($P=0.7$).

Biweekly spirometry showed no difference between the three regimens for either forced vital capacity, FEV₁, or forced expiratory flow at 25–75 of vital capacity (Table 2).

For safety reasons, the exercise challenge was not performed at the completion of a 4 week regimen if baseline FEV₁ was less than 65% of predicted. Thus, 19 subjects completed exercise challenge on placebo, 17 during nifedipine and 18 during diltiazem. Only 12 subjects completed exercise studies after all three regimens (Table 3). Exercise workload as measured by oxygen consumption and minute ventilation were not significantly different between treatments, but heart rate was significantly higher on nifedipine (162 ± 11 beats min⁻¹) and lower on diltiazem (135 ± 2 beats min⁻¹) compared with placebo (145 ± 3 beats min⁻¹) ($P=0.03$). In the 12 subjects who completed all three exercises challenges, the maximum decrease in post-exercise FEV₁ was $31 \pm 5\%$ after placebo, $30 \pm 5\%$ after nifedipine and $25 \pm 4\%$ after diltiazem ($P=0.5$).

Figure 1 The mean ($\pm$ s.e. mean) percent days when subjects experienced symptoms of nocturnal asthma that woke them, asthma symptoms that interfered with daytime activities such as going to school or work, and when wheezing or coughing was present. There was no significant difference between treatments for any of these subjective endpoints. ■ placebo, ▨ nifedipine, □ diltiazem.

Figure 2 The mean (●) ($\pm$ s.e. mean) daily peak expiratory flow measured in the morning upon arising, before the dose of study medication, and the mean (■) ($\pm$ s.e. mean) in the evening, before the bedtime dose, for each of the three treatments. The numbers on the x-axis represent the number of days on each treatment. There were no significant differences between treatments.

Table 2 Average of spirometric values during the last three weeks of each treatment.

	Placebo	Diltiazem	Nifedipine
FVC (l)	3.86 ± 0.07	3.98 ± 0.08	3.95 ± 0.09
% predicted	$79 \pm 1\%$	$81 \pm 1\%$	$81 \pm 2\%$
FEV ₁ (l)	3.06 ± 0.05	3.08 ± 0.06	3.09 ± 0.07
% predicted	$80 \pm 2\%$	79 ± 2	80 ± 2
FEF ₂₅₋₇₅ (l s ⁻¹)	2.73 ± 0.13	2.67 ± 0.13	2.76 ± 0.15
% predicted	$66 \pm 4\%$	$64 \pm 4\%$	$66 \pm 4\%$

Intervention with a short course of oral prednisone for bronchodilator unresponsive symptoms was required by two subjects during nifedipine, by two different subjects during diltiazem treatment, but none of the subjects required prednisone during placebo.

In contrast, significant differences between regimens were noted in biweekly cardiovascular measurements, with heart rate significantly elevated during nifedipine administration and P-R interval of the electrocardiogram significantly prolonged during diltiazem (Table 4). No significant alteration in blood pressure was noted on either active regimen.

Discussion

The results of this study indicate that maintenance therapy with nifedipine or diltiazem, at doses producing measurable cardiovascular effects, did not improve asthma

Table 3 Response to the standardized exercise challenge.

Response	Placebo	Diltiazem	Nifedipine
Subjects completing at least one challenge (N)*	19	18	17
Oxygen consumption (ml kg ⁻¹ min ⁻¹)	28 ± 2	29 ± 2	28 ± 2
Mean percentage Δ FEV ₁	-32 ± 4	-27 ± 3	-32 ± 4
Subjects completing all three challenges (n)	12	12	12
Oxygen consumption (ml kg ⁻¹ min ⁻¹)	28 ± 2	27 ± 1	27 ± 2
Mean percentage Δ FEV ₁	-31 ± 5	-25 ± 4	-30 ± 5

*Subjects with an FEV₁ < 65% did not perform the exercise challenge for safety reasons.

Table 4 Average cardiovascular parameters during the last 3 weeks of each treatment.†

	Placebo	Diltiazem	Nifedipine	P value
Blood pressure (mmHg)				
systolic	113 ± 1	116 ± 2	114 ± 1	NS
diastolic	70 ± 1	70 ± 1	67 ± 1	
Heart rate (beats min ⁻¹)	75 ± 2	72 ± 2	83 ± 2	0.0001
P-R interval	0.165 ± 0.003	0.178 ± 0.003	0.160 ± 0.002	0.0001

†Cardiovascular parameters were within normal limits for all subjects during the screening visit, a requirement for entrance into the study.

symptoms or lung function and did not decrease the need for rescue medication or reduce airway responsiveness to exercise in this group of young adults with mild-moderate persistent asthma. The results for diltiazem are not surprising. It was our hypothesis that bronchoprovocation studies could be used to predict the efficacy of maintenance therapy with calcium channel blockers and diltiazem was consistently ineffective in attenuating airway responsiveness to either methacholine [10, 28] or exercise [8, 10]. Even when high doses were delivered to the airways directly by nebulization, diltiazem did not attenuate the response to either bronchoprovocation [14].

In contrast, we were surprised to find that nifedipine did not decrease airway responsiveness to exercise. In most previous studies this drug attenuated exercise-induced bronchospasm, although the degree of benefit varied markedly between studies [4, 5, 7, 11, 25–27]. All of them employed a single dose design whereas our exercise challenge was performed after 4 weeks of multiple dose therapy. It is possible that tachyphylaxis to the bronchoprotective effect of nifedipine developed, an effect commonly seen with β_2 -selective adrenergic agonists [33, 34], but tolerance does not appear to develop to the haemodynamic effects of nifedipine [35, 36].

Another possible explanation for the difference in exercise results may be how treadmill workload was targeted. In previous reports, a target heart rate was used to adjust the speed and incline of the treadmill. However, as demonstrated in the present study, nifedipine significantly increases heart rate. Therefore, in adjusting the treadmill to give the same target heart rate, the workload on the nifedipine treatment day would have been less than on the placebo day. This, in turn, would produce less stimulus for exercise-induced bronchospasm and, a smaller decrease in FEV₁ post-exercise giving specious results that nifedipine was attenuating exercise-induced bronchospasm. In contrast, in our study we adjusted the treadmill conditions to produce the same minute ventilation and oxygen consumption, and, thus, our subjects received the same workload on each study day.

Patients with asthma have increased airway responsiveness to a variety of stimuli. When external stimuli trigger an increase in calcium ion concentration in the cytosol of airway smooth muscle cells, the muscle contracts [3]. If enhanced calcium ion mobilization is the mechanism underlying airway responsiveness, then why wasn't nifedipine effective in reducing the signs and symptoms of asthma in our subjects? Firstly, nifedipine primarily blocks voltage-operated channels whereas increased intracellular calcium ion concentrations also may result from influx *via* receptor-channels and by release of calcium ions from intracellular stores [2]. These alternative sources may provide enough calcium ions to continue airway muscle contractility in the presence of nifedipine.

Secondly, nifedipine may have greater specificity for cardiac tissue. *In vitro*, the concentration required to inhibit tracheal muscle contraction or relax precontracted muscle is much higher than in vascular smooth muscle [37]. This could be a result of different receptors for calcium channel blockers in respiratory and cardiac muscle or lower affinity for receptors in respiratory muscle [2]. Since cardiovascular effects limit the dose of these drugs, it is not possible to give doses that could produce sufficient concentration in airway muscles to exert a clinically beneficial effect.

In conclusion, the results of the present study, when taken together with other published reports, clearly indicate that calcium channel blockers are not clinically effective as maintenance therapy for persistent asthma. The results for nifedipine could not have been predicted from previous bronchoprovocation studies. However, there is no evidence in this or other studies that calcium channel blockers worsen asthma when given orally and therefore they can be safely used in the treatment of angina, hypertension or migraine headache in a patient with asthma where β -adrenoceptor blockers are relatively contraindicated.

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