Comparison of PY 108-068, a New Calcium Antagonist, with Nifedipine in Exercise-Induced Asthma*

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Several calcium antagonists, each with significantly different chemical structures, have demonstrated variable attenuation of exercise-induced asthma. Quantitative comparisons have been hampered by differences in the intensity of challenge and the severity of the underlying disease between groups of patients. In 12 asthmatic adults with relatively severe exercise-induced asthma, we compared the effect of a new calcium antagonist, PY 108-068, in doses of 75 mg and 150 mg with nifedipine (30 mg) and placebo on resting flow rates and flow rates after exercise. Over a three-week period, each patient completed a four-day, randomized, double-blind Latin-square study. After receiving one of four oral drugs, spirometry was repeated every 30 minutes for two hours, followed by a six-minute treadmill exercise test breathing dry air. The exercise tests were well matched for work rate, ventilation, heart rate, and oxygen uptake. Spirometry was then repeated seven times over the next 30 minutes after exercise. Though both 150 mg of PY 108-068 and nifedipine were associated with mild bronchodilation before exercise, only the latter was significant (p<0.05). Exercise-induced asthma (expressed as maximal percent fall in the forced expiratory volume in one second from before baseline) was significantly attenuated only by 150 mg of PY 108-068 compared to placebo (24 ± 13 vs 40 ± 16; p<0.05). Headache, which occurred in six subjects after nifedipine, five after 150 mg of PY 108-068, one after 75 mg of PY 108-068, and none after placebo, was subjectively more severe after nifedipine. We conclude that in these patients, there was a tendency for mild bronchodilation before exercise with both 150 mg of PY 108-068 and nifedipine, but only the 150-mg dose provided significant protection against exercise-induced asthma two hours after the drug.

Many of the pathophysiologic events underlying asthma, including contraction of bronchial smooth muscle and degranulation of mast cells, are calcium-dependent. Because of this, studies have been done to determine the effect of calcium antagonists on pulmonary function in asthmatic subjects. These studies have measured the effect of these drugs on flow rates at rest and after various challenges including antigen, histamine, hyperventilation, and exercise. Exercise has frequently been used because it is safe, natural, and reproducible and has short-term effects; however, the reported effects of calcium antagonists on exercise-induced asthma have varied from complete prevention of bronchospasm to only mild attenuation. Similarly, reported effects on resting bronchodilation vary from none to bronchodilation comparable to isoproterenol. Possible reasons for the lack of agreement among these studies include differences in protocols, differences in the severity of underlying disease between groups of subjects, and inherent differences in the various calcium antagonists; for example, the calcium antagonists, nifedipine, verapamil, and diltiazem, each display unique cardiovascular effects. Thus, while it would not be surprising if such agents also exhibited differences in their effect on exercise-induced asthma, there have been no reported comparisons of calcium antagonists in the same individual. The purpose of this study was to compare the effect on resting bronchodilation and on exercise-induced asthma of a new calcium antagonist, PY 108-068, with nifedipine and placebo in the same subjects.

Materials and Methods

We studied 16 asthmatic volunteers (nine women and seven men) ranging in age from 18 to 52 years (mean of 33 years). We obtained approval of the study from the human subject committee at our institution, and each patient gave informed consent. Preliminary evaluation included history and physical examination, complete blood cell count, electrolyte levels, tests of renal and hepatic function, urinalysis, electrocardiogram, and chest roentgenogram to exclude subjects with systemic disease other than asthma. Recent respiratory tract infection or use of corticosteroids or cromolyn sodium within the past three months also served as criteria for exclusion. Physiologic tests included spirometry before and after four breaths of a 0.5 percent solution (1:200) of isoproterenol using a 9-L spirometer (Warren E. Collins) and a six-minute treadmill exercise test to assess exercise-induced asthma. All subjects accepted had both an increase in the forced expired volume in one second (FEV1) of at least 15 percent after isoproterenol, compared to their immediate baseline before isoproterenol, and a fall in FEV1 of at least 20 percent after exercise, compared to their baseline before...
exercise. The baseline FEV\textsubscript{1} in percent of predicted for the subjects ranged from 108 percent to 94 percent with a mean ± SD of 88 ± 16 percent.

The study consisted of four testing days, each separated by at least 24 hours. Testing occurred at the same time each day for an individual subject and was completed within a three-week period. Throughout the study, subjects were maintained on their prescribed medications for asthma except that all medication was withheld for six hours prior to study. On each testing day, after obtaining blood pressure, pulse rate, and baseline spirometric data, a subject received one of the following four oral drugs in a randomized double-blind order: (1) 75 mg of PY 108-068; (2) 150 mg in PY 108-068; (3) 30 mg of nifedipine; or (4) placebo. Spirometry was repeated every 30 minutes for two hours, at which time blood pressure and pulse rate were again measured. The subject then ran on the treadmill for six minutes at a work rate estimated to achieve approximately 70 percent of his or her maximum oxygen uptake. The appropriate work rate was determined at each individual's screening test. To ensure standard air conditions and to increase the bronchoconstrictive effect of exercise, dry compressed air was inhaled for two minutes before and throughout the period of exercise. Subjects breathed through a mouthpiece with a small dead space and breathing valve (Koegel).

The exhalation port was attached to a pneumotachygraph (Fleisch No. 3) and a flow transducer (Hewlett-Packard 473904A). Gas was sampled at the mouthpiece for continuous measurement of fractional concentrations of exhaled oxygen and carbon dioxide using a mass spectrometer (Perkin-Elmer MCA-1100). A microcomputer (Hewlett-Packard 9825A) was used for on-line measurement and printout of various cardiorespiratory variables as described previously. An ECG continuously measured heart rate and rhythm. The FEV\textsubscript{1} at two hours after the drug was considered the baseline before exercise. Spirometry was repeated at 3, 6, 10, 15, 20, 25, and 30 minutes after exercise. We reported the amount of exercise-induced asthma as the maximal percentage of fall in FEV\textsubscript{1} from baseline before exercise.

At the end of the study, a full evaluation identical to that of the screening was repeated in order to detect any abnormalities which might be caused by the calcium antagonists. Results were analyzed by analysis of variance. If a significant difference was found, then individual mean differences were identified using the Scheffé test.

Results

Twelve of 16 subjects completed the study. Four subjects dropped out after the first day (two due to exacerbations of asthma thought unrelated to the study, one due to lack of cooperation, and one due to an unrelated illness).

Resting bronchodilation, expressed as mean percentage of change in FEV\textsubscript{1} from baseline, is shown in Figure 1. The peak bronchodilator effect of nifedipine occurred at one-half and one hour, while that for 150 mg of PY 108-068 occurred two hours after administration of the drug. Only nifedipine caused a significant increase in FEV\textsubscript{1} as compared to placebo by the Scheffé test.

The increase in heart rate above baseline at two hours was significantly more after taking 150 mg of PY 108-068 (16 ± 4 beats per minute; mean ± SD), as compared to 75 mg (2 ± 2 beats per minute), nifedipine (5 ± 2 beats per minute), and placebo (–3 ± 2 beats per minute). Systolic blood pressure did not vary significantly among the four drugs. Diastolic blood pressure decreased significantly two hours after 75 mg of PY 108-068 (–8 ± 3 mm Hg) and after 150 mg (–9 ± 3 mm Hg), compared to placebo (4 ± 2 mm Hg). Diastolic blood pressure after 150 mg of PY 108-068 was also significantly lower than after nifedipine (–6 ± 3 mm Hg) at two hours after the drug.

All subjects completed the exercise protocol. The stimulus for bronchospasm was the same in that there were no differences in the maximum minute ventilation, heart rate, and maximum oxygen uptake achieved on each occasion. Bronchospasm and dyspnea were evident after nearly every bout of exercise, with maximal reduction in flow rates 6 to 15 minutes after cessation of exercise. Only the mean percentage of change in FEV\textsubscript{1} after 150 mg of PY 108-068 (24 ± 13) was significantly less than placebo (40 ± 16). The maximum falls in FEV\textsubscript{1} after exercise for 75 mg of PY 108-068 and

![Figure 1. Percentage of change in FEV\textsubscript{1}, before exercise (mean ± SE; N = 12) from baseline at 30, 60, 90, and 120 minutes after nifedipine (squares), placebo (triangles), 150 mg of PY 108-068 (diamonds), and 75 mg of PY 108-068 (circles).]

Table 1—Maximal Percentage of Change in FEV\textsubscript{1}, after Exercise

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<tr>
<th>Subject</th>
<th>Placebo</th>
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<th>PY108-068 150 mg</th>
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Mean ± SD

| 40 ± 16 | 26 ± 15 | 24 ± 13 | 29 ± 11 |
nifedipine were 26 ± 15 and 29 ± 11, respectively; individual changes in FEV₁ associated with each drug are shown in Table 1.

Headache was a frequent side effect, occurring in six subjects after nifedipine, five after 150 mg of PY 108-068, one after 75 mg of PY 108-068, and none after placebo. It was subjectively more severe after nifedipine. One subject complained of palpitations and another complained of lightheadedness 30 minutes after taking nifedipine. No significant laboratory abnormalities were detected at the end of the study.

**DISCUSSION**

Bronchodilation and prevention of exercise-induced asthma are separate and useful goals of therapy for asthma. We studied a class of drugs that may have potential for meeting either or both of these goals.

We found some resting bronchodilation associated with both 150 mg of PY 108-068 and nifedipine, although only the latter was significant. Some studies on calcium antagonists in asthma have not shown resting bronchodilation; however, measurements were only made up to 30 minutes and 45 minutes after dosing. Patakas et al. extended measurements up to two hours and did find significant resting bronchodilation with nifedipine. PY 108-068, which, according to some, is the most potent calcium antagonist presently known, has recently been studied by Ben-Dov et al. They found a significant increase in resting FEV₁ (15 percent with 150 mg of PY 108-068 vs 3 percent with placebo), which occurred at a mean of 143 ± 20 minutes after the 150 mg. These data plus the increasing FEV₁ after 150 mg of PY 108-068 shown in Figure 1 suggest that bronchodilation after 150 mg of PY 108-068 may have become apparent in our study if the time of measurement had been extended.

Another possibility is that the differences in resting flow rates found between placebo and calcium antagonists represent not bronchodilation by calcium antagonists but rather inhibition of deep inspiration-induced bronchospasm. Bronchospasm caused by repeated deep breaths would explain both the progressive fall in FEV₁ before exercise with placebo and the initial decrease in FEV₁ seen with 75 mg and 150 mg of PY 108-068. Because nifedipine has a more rapid onset of action, the deep inspiration-induced bronchospasm could have been prevented altogether. Three subjects did complain that the maneuvers made them wheeze. Of note, nifedipine has been shown previously to inhibit deep inspiration-induced bronchospasm in asthmatic subjects. The mechanism underlying this type of bronchospasm is not known, but one theory is that pulmonary irritant receptors, which are abnormally sensitive in asthmatic subjects, are stimulated by nonspecific irritants, such as deep inspiration, resulting in cholinergic bronchoconstriction. It is known that calcium antagonists block influx of calcium into the tracheal smooth muscle, thus inhibiting the constriction induced by low doses of acetylcholine; however, whether or not the protective effect of the calcium antagonists resides at the level of the bronchial smooth muscle is not known.

In regard to the protection against exercise-induced asthma, both nifedipine and 150 mg of PY 108-068 have been shown to attenuate exercise-induced asthma in previous studies; however, comparison of these drugs is hampered by differences in protocols and in the severity of underlying disease between groups of subjects. We attempted to control for all variables except the drugs, thereby allowing direct comparison of their effects on exercise-induced asthma. Carefully standardized conditions in which the degree of exercise was matched closely for each subject on all four testing days assured that the stimuli for bronchospasm were always the same. Because placebo itself can significantly reduce exercise-induced asthma, nifedipine and PY 108-068 were compared to placebo. Each subject served as his own control, thus eliminating individual differences among subjects which might alter a drug’s effect. Both nifedipine and PY 108-068 were given at the recommended therapeutic dosage. The high incidence of headache associated with nifedipine would limit any increase in dosage.

The calcium antagonists are a heterogeneous group of drugs, both in their structure and their pharmacologic effects; for example, nifedipine, a potent vasodilator, is very effective in relieving angina caused by coronary vasospasm but has little effect on the atrioventricular node. Verapamil, on the other hand, significantly prolongs conduction through the atrioventricular node and is the drug of choice for reentrant supraventricular tachycardias. The calcium antagonists’ diverse structures and their stereoselectivity suggest that they may bind to different sites in the calcium channel and have different modes of action. Nifedipine may act by "plugging" the calcium channels, whereas verapamil may be "use-dependent;" that is, as the use or frequency of contraction of the muscle increases, the force of contraction decreases. Much remains to be learned about how these drugs block the calcium channels, but considering their dissimilar cardiovascular effects, one might also expect differences in their effect on the airways.

Indeed, we found that 150 mg of PY 108-068 was superior to nifedipine in protection against exercise-induced asthma; however, surprisingly, nifedipine was not significantly better than placebo. This result differs from that of several other published studies. A possible explanation for nifedipine’s lack of protection in our study involves the timing of exercise. In order to assure a double-blind protocol, all exercise testing was done two hours after dosing. If nifedipine’s peak effect
occurred 30 minutes after the dose, the time when most of the studies showing significant protection were done, then its maximal protection may have been missed. Unfortunately, the time at which maximal effect occurs for these drugs is not known. The time for each drug's maximal effect may vary among individuals, depending on their rates of absorption.

In conclusion, only nifedipine produced significant resting bronchodilation and only 150 mg of PY 108-068 provided significant protection against exercise-induced asthma. The time of testing may have contributed to both results. In either case, the effects of these calcium antagonists on both resting bronchodilation and protection against exercise-induced asthma are mild. Based on the physiologic role of calcium in asthma, the calcium antagonists may still eventually play a role in therapy. Because β-sympathomimetics are more effective in exercise-induced asthma by inhalation than by the oral route, the effect of inhaled calcium antagonists should be assessed. As more calcium antagonists are developed, one that is more capable of preventing exercise-induced asthma may be found.

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