

# The effect of inhaled gallopamil, a potent calcium channel blocker, on the late-phase response in subjects with allergic asthma

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*The effect of gallopamil on the late-phase response to inhaled allergen was evaluated in six young adults with allergic asthma in a crossover manner. During 2 study days, subjects received 20 mg of inhaled gallopamil or placebo 30 minutes before challenge with the same dose of allergen. In addition, a histamine challenge was performed 1½ hours before and 24 hours after allergen challenge. On 2 additional study days, in the absence of allergen, basal airway responsiveness to histamine was measured before and after gallopamil or placebo administration. During the early phase, the mean  $\pm$  SD decrease in FEV<sub>1</sub> was 28.0%  $\pm$  11.3% after placebo and 25.1%  $\pm$  8.4% after gallopamil administration ( $p > 0.05$ ;  $\beta = 0.14$ ). During the late phase, the maximum decrease in FEV<sub>1</sub> was 26.9%  $\pm$  11.9% after placebo and 25.3%  $\pm$  10.3% after gallopamil administration ( $p > 0.05$ ;  $\beta = 0.21$ ). Airway reactivity to histamine 24 hours after allergen challenge could not be measured in three subjects after gallopamil administration and in one subject after placebo administration because of persistent bronchospasm. In contrast, basal responsiveness to histamine in the absence of allergen was modestly decreased by gallopamil. Since gallopamil is one of the most potent calcium channel blockers when it is administered by the inhaled route, it is unlikely that this group of drugs will be clinically useful for allergic asthma. (J ALLERGY CLIN IMMUNOL 1992;89:688-95.)*

**Key words:** Gallopamil, calcium channel blocker, late phase, allergic asthma

Inhalation of allergen in sensitive subjects with asthma may produce an early, as well as an LPR, several hours after allergen administration. Since mast cell release of mediators,<sup>1</sup> biosynthesis of leukotrienes<sup>2</sup> and inflammatory cell migration<sup>3</sup> are calcium-dependent processes, it is tempting to speculate that this class of drugs might attenuate the development of the LPR to inhaled allergen in humans. This hypothesis is supported by evidence in the sheep

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## Abbreviations used

|                    |                                                                                                         |
|--------------------|---------------------------------------------------------------------------------------------------------|
| LPR:               | Late-phase response                                                                                     |
| $\beta$ :          | Beta statistical error; the probability of missing a treatment effect because of inadequate sample size |
| MDI:               | Metered-dose inhaler                                                                                    |
| GM:                | Geometric mean                                                                                          |
| GSD:               | Geometric standard deviation                                                                            |
| PC <sub>20</sub> : | Provocative concentration of histamine causing a 20% decrease in FEV <sub>1</sub>                       |
| PD <sub>20</sub> : | Cumulative dose of allergen causing a 20% decrease in FEV <sub>1</sub> during the early phase           |
| SG <sub>aw</sub> : | Specific airway conductance                                                                             |

model of allergic asthma in which verapamil<sup>4</sup> and gallopamil<sup>5</sup> inhibited the LPR to inhaled allergen.

The protective effect of calcium channel blockers against allergen-induced bronchoconstriction has been evaluated in several studies with conflicting results. So et al.,<sup>6</sup> for example, were unable to demonstrate significant attenuation of the early phase response to inhaled allergen in eight atopic subjects with asthma with either nebulized verapamil (2.4 mg) or sublingual

**TABLE I.** Pulmonary function, basal airway responsiveness to histamine, and inhaled allergen on prestudy qualifying day and inhaled bronchodilator use before the study

| Subject | Age/sex (yr) | FEV <sub>1</sub> on qualifying day (% predicted) | Histamine PC <sub>20</sub> on qualifying day (mg/ml) | Allergen                | Allergen PD <sub>20</sub> (AU) | History of inhaled $\beta$ -agonist use (No. doses) |
|---------|--------------|--------------------------------------------------|------------------------------------------------------|-------------------------|--------------------------------|-----------------------------------------------------|
| 1       | 18/F         | 96                                               | 4.2                                                  | <i>D. farinae</i>       | 31                             | 2/wk                                                |
| 2       | 25/M         | 68                                               | 3.2                                                  | <i>Alternaria</i>       | 440 (PNU)                      | 3/day                                               |
| 3       | 19/F         | 80                                               | 4.2                                                  | <i>D. farinae</i>       | 83                             | 2/wk                                                |
| 4       | 24/F         | 92                                               | 4.4                                                  | Timothy grass           | 54                             | 2/wk                                                |
| 5       | 20/M         | 85                                               | 9.0                                                  | Cat hair/epith          | 2116                           | 3/wk                                                |
| 6       | 19/M         | 82                                               | 12.0                                                 | <i>D. pteronyssinus</i> | 32                             | 1/mo                                                |
| Mean    | 21           | 84                                               | 5.5*                                                 |                         |                                |                                                     |
| SD      | 2.9          | 9.9                                              | 1.7                                                  |                         |                                |                                                     |

PNU, Protein nitrogen unit; *epith.*, epithelium.\*GM  $\pm$  GSD.

nifedipine (20 mg). In contrast, Russi et al.<sup>7</sup> demonstrated that oral nifedipine (20 mg) was effective in attenuating the early response to allergen and was more potent than oral verapamil (160 mg). In a subsequent study, this group of investigators demonstrated that inhaled verapamil attenuated the early response to allergen to a greater extent than the oral route.<sup>6</sup> These data, taken together, suggest that the efficacy of this pharmacologic class of drugs in attenuating allergen-induced bronchoconstriction is a function of drug, dose, and route of administration.

Gallopamil is a methoxy derivative of verapamil. It is 10 to 20 times more potent than verapamil in relaxing carbachol-induced contraction of sheep tracheal strips<sup>9</sup> and has consistently demonstrated modest effectiveness in attenuating exercise<sup>10-12</sup> and methacholine-induced bronchoconstriction<sup>11, 13</sup> in humans. In addition, the results of one study in subjects with allergic asthma suggest that 10 mg of inhaled gallopamil is as effective as cromolyn in preventing the early phase response to allergen.<sup>14</sup>

In all of the human studies of the effect of calcium channel blockers on allergen-induced bronchoconstriction to date, only the early phase response has been evaluated. This response alone, however, may not account for the clinical features of chronic asthma. Cockcroft<sup>15</sup> has suggested that the LPR and subsequent development of increased airway reactivity (markers of airway inflammation) more closely correspond to the natural course of chronic asthma.

Therefore, the present study was conducted to determine whether gallopamil, a potent calcium channel blocking agent, administered by the nebulized route in the highest tolerated dose, would attenuate allergen-induced inflammation of the airways in volunteers with mild allergic asthma.

## METHODS

### Subject selection

Six subjects (three were male), aged 18 to 25 years (mean, 21 years), with a documented dual pulmonary function response to inhaled allergen, were enrolled in the study. To qualify, FEV<sub>1</sub> in subjects had to decrease  $\geq 20\%$  from baseline during the first hour (early phase) and at least 15%, 3 to 8 hours after allergen (late phase). Each subject had a history of mild intermittent asthma with an increase in symptoms that correlated with an increase in the presence of inhaled allergens in the air, vacuuming, first seasonal use of central heating, or exposure to a known allergen (e.g., cats). None of the subjects required oral or inhaled corticosteroids, emergency room visits, or hospitalizations for asthma in the 60 days before entry into the study, and none had symptoms of a viral upper respiratory tract infection at least 30 days before or during the study.

On each study day, subjects were required to have an FEV<sub>1</sub> within 90% to 110% of the value on their qualifying day and at least 65% of predicted for age, sex, and height.<sup>16</sup> PC<sub>20</sub> had to be  $\leq 16$  mg/ml before the study and within a two-fold concentration on subsequent study days (Table I). Inhaled albuterol<sup>17</sup> or terbutaline<sup>18</sup> by MDI were withheld for at least 6 hours and isoproterenol by MDI for at least 2 hours<sup>19</sup> before histamine challenges on each study day. None of the subjects were taking other medications or had other conditions known to alter airway reactivity.<sup>20</sup>

Studies were conducted at the same time of day in the same laboratory in which temperature, humidity, and ventilation were kept constant. Subjects who were sensitive to molds or pollen were studied when the allergen was unlikely to be present in ambient air.

The protocol was approved by the University of Florida Health Center Institutional Review Board, and written informed consent was obtained from each subject.

### Gallopamil administration

Gallopamil powder (Key Pharmaceuticals, Miami, Fla.) was dissolved in 0.45% saline containing a final concen-

tration of 10% ethanol and 2% propylene glycol to solubilize the drug. The placebo was the diluent alone. A 20 mg dose in 3 ml volume was administered during 10 to 12 minutes of tidal breathing from a Hudson Up-draft II nebulizer (Hudson Respiratory Care, Inc., Temecula, Calif.) driven by a DeVilbiss air compressor (DeVilbiss Co., Somerset, Pa.) at an effective flow rate of 4 L/min. The mean  $\pm$  SD output of this nebulizer was  $0.267 \pm 0.15$  ml/min with an aerodynamic mass median diameter of 4.6 (GSD of 4.2).<sup>11</sup> Since the stability of gallopamil in this extemporaneously prepared solution was unknown, each dose was prepared immediately before administration.

### Spirometry

Spirometry, measured by a Collins survey spirometer (Warren E. Collins, Braintree, Mass.), consisted of FEV<sub>1</sub>, FVC, and forced expiratory flow rate between 25% and 75% of FVC. The best of three attempts was recorded and expressed as a percent predicted for age, height, and sex.<sup>16</sup>

### Bronchoprovocation

**Histamine.** Histamine bronchoprovocation was performed by a modification<sup>11</sup> of the tidal breathing method according to Cockcroft et al.<sup>21</sup> Twofold increasing concentrations of histamine were administered from a calibrated (0.13 ml/min) Wright nebulizer (Roxon MediTech, Montreal, Canada) at 5-minute intervals until FEV<sub>1</sub> decreased by >20%. The concentration of histamine required to produce a 20% decrease in FEV<sub>1</sub> (PC<sub>20</sub>) was interpolated graphically from the last two data points of the plot of percent change in FEV<sub>1</sub> and log<sub>e</sub> concentration of histamine.

**Allergen.** Allergen bronchoprovocation was performed by the tidal breathing method according to that described by Cockcroft and Murdock.<sup>22</sup> The number of allergy units or protein nitrogen units in the case of *Alternaria* that was delivered was calculated from the output of the nebulizer (0.13 ml/min), the concentration of the solution, and the duration of nebulization (2 minutes of tidal breathing).

The allergen solutions were freshly prepared each study day from bulk extracts diluted with a bicarbonate-buffered saline (Albay; Hollister-Stier Laboratories, Spokane, Wash.) The extracts included *Dermatophagoides farinae* and *D. pteronyssinus* (Berkeley Biologicals, Berkeley, Calif.), timothy grass and cat hair/epithelium (Hollister-Stier Laboratories), and *Alternaria tenuis* (Greer Laboratories, Lenoir, N.C.). All the allergens except *Alternaria*, were standardized products.

The allergen was selected for bronchoprovocation on the basis of results of cutaneous prick tests that correlated with clinical history. Before the first allergen challenge, on a separate day, serial dilutions of the selected allergen were applied by cutaneous pricks to determine the lowest concentration of allergen that produced a 2 mm wheal. Three twofold dilutions of this concentration were then used as the initial dose for bronchoprovocation on the qualifying day. After inhalation of diluent alone, the initial dose was administered during a 2-minute period, and spirometry was performed at 5-minute intervals until the FEV<sub>1</sub> stabilized. This process was repeated with twofold increasing concentrations of allergen until FEV<sub>1</sub> decreased by >20%. The

PD<sub>20</sub> was interpolated graphically from the last two data points of the plot of percent change in FEV<sub>1</sub> and log<sub>e</sub> cumulative dose of allergen.

On 2 subsequent study days, allergen-inhalation challenge was performed with the PD<sub>20</sub> dose of allergen determined from the qualifying allergen challenge. To avoid an unanticipated large decrease in FEV<sub>1</sub>, the allergen dose was administered in three equal aliquots at 10-minute intervals. Spirometry was performed at 5 and 10 minutes after each aliquot, and if FEV<sub>1</sub> decreased by >20% from baseline, two puffs of isoproterenol were administered by MDI. After isoproterenol administration, spirometry was performed at 5-minute intervals until FEV<sub>1</sub> returned to 80% of baseline. The remaining aliquot(s) of allergen were then administered so that each subject received the same total dose of allergen on both study days. This procedure allowed the same allergen stimulus for the late phase on each study day. Two previous studies have demonstrated that administration of inhaled  $\beta$ -antagonists either before or during allergen challenge does not block the late phase.<sup>22,23</sup> After administration of the third aliquot of allergen, spirometry was performed at 5, 10, 15, 30, 45, 60, 90, and 120 minutes and hourly thereafter until the decrease in FEV<sub>1</sub> stabilized, or reached 50% or less of predicted, or the patient requested treatment with a bronchodilator to relieve symptoms. Nebulized albuterol, 2.5 mg in 3 ml saline, was then administered at 20-minute intervals until FEV<sub>1</sub> returned to baseline for the study day. Subjects were discharged from the laboratory with an albuterol or terbutaline MDI to use as needed, an Assess peak flow meter (Health Scan Products, Cedar Grove, N.J.), and a supply of prednisone tablets to be used only after contact with the physician investigator. Subjects were required to call us if symptoms and/or peak expiratory flow rate became unresponsive to the inhaled  $\beta$ -agonist therapy.

### Experimental design

Subjects attended the bronchoprovocation laboratory five times, each at least 7 days apart. Day 1 was a qualifying day consisting of spirometry, a histamine challenge, and then an allergen challenge at least 1½ hours later. Days 2 through 5 each began with spirometry and a histamine challenge to determine whether the PC<sub>20</sub> was within one twofold concentration of the value obtained on the qualifying day and whether FEV<sub>1</sub> was 90% to 110% of the value measured on the qualifying day. Subjects were rescheduled for another day when these criteria were not met.

On days 2 and 3, gallopamil and placebo were administered at least 1 hour after histamine challenge when FEV<sub>1</sub> was  $\geq 90\%$  of the baseline of that day. Then, 30 minutes after treatment, the allergen challenge was begun. Subjects returned to the laboratory for a second histamine challenge 24 hours after the allergen challenge to measure increased airway reactivity. Placebo was always administered on study day 3 so that response to allergen could be compared before and after the study day with active drug (day 2). This was done to detect any consistent change in response to allergen that might result from receiving three allergen challenges, that is, increased or decreased sensitivity to the allergen.

On days 4 and 5, no allergen was administered. Gal-

lopamil or placebo was administered in a randomized, cross-over manner at least 1 hour after the baseline histamine challenge (when FEV<sub>1</sub> returned to 90% of baseline). Then, 30 minutes after treatment, the histamine challenge was repeated. An interval of 1½ hours between challenges is sufficient to circumvent tachyphylaxis to histamine.<sup>17,24</sup> The purpose of these 2 study days was to determine whether gallopamil attenuates basal airway responsiveness to histamine, that is, the nonspecific airway reactivity found in subjects with asthma in the absence of an allergen challenge.

The study was a single-blinded design. The subjects were unaware of whether they were receiving gallopamil or placebo on study days 2 to 5, but the primary investigator (M. H.) prepared the solutions immediately before administration.

### Statistical analysis

Mean values for FEV<sub>1</sub> and histamine PC<sub>20</sub> at the beginning of each of the 5 study days were compared with the non-parametric Friedman's analysis of variance by ranks.<sup>25</sup> Differences in mean values for maximum decrease in FEV<sub>1</sub> for the early and late phases and the GM fold increase in PC<sub>20</sub> on study days 4 and 5 were evaluated with a Wilcoxon's signed-rank test.<sup>26</sup> Results were considered statistically significant at  $\alpha = 0.05$  and expressed as mean  $\pm$  SD, or GM  $\pm$  GSD in the case of allergen PD<sub>20</sub> and histamine PC<sub>20</sub>.

### RESULTS

All subjects completed the 5 study days. On the prestudy qualifying day, mean baseline FEV<sub>1</sub> was 84% of predicted, and the geometric mean baseline histamine PC<sub>20</sub> was 5.5 mg/ml (Table I). There was no consistent change in LPR between the first challenge on the qualifying day (study day 1) and the third challenge on the placebo-treatment day (Table II).

Gallopamil did not significantly attenuate either the early or LPRs to allergen (Fig. 1). The mean  $\pm$  SD maximum decrease in FEV<sub>1</sub> during the early phase was 28.0%  $\pm$  11.3% after placebo administration and 25.1%  $\pm$  8.4% after gallopamil administration ( $p > 0.05$ ;  $\beta = 0.14$  for a 50% difference between treatments). These values may be an underestimation of the maximum decrease in FEV<sub>1</sub> during the early phase, since three subjects received inhaled isoproterenol during allergen challenge so that the same total dose could be administered on both study days. Subject No. 1 required isoproterenol during the gallopamil-treatment study day, subject No. 3 required isoproterenol during the placebo-treatment day, and subject No. 2 required isoproterenol on both study days (Fig. 1).

The mean  $\pm$  SD maximum decrease in FEV<sub>1</sub> during the late phase was 26.9%  $\pm$  11.9% after placebo treatment and 25.3%  $\pm$  10.3% after gallopamil treatment ( $p > 0.05$ ;  $\beta = 0.21$  for a 50% difference between treatments). In subject No. 1, gallopamil was markedly more effective than placebo in attenuating

**TABLE II.** Comparison of the LPR on 2 study days without premedication

| Subject | Maximum % decrease in FEV <sub>1</sub> |                               |
|---------|----------------------------------------|-------------------------------|
|         | Qualifying day<br>(study day 1)        | Placebo day*<br>(study day 2) |
| 1       | 33.6                                   | 48.8                          |
| 2       | 31.2                                   | 24.5                          |
| 3       | 27.9                                   | 28.6                          |
| 4       | 25.4                                   | 14.4                          |
| 5       | 40.4                                   | 19.1                          |
| 6       | 18.7                                   | 26.2                          |
| Mean    | 29.5                                   | 26.9                          |
| SD      | 7.4                                    | 11.9                          |

\*On the qualifying day, the dose of allergen was titrated until FEV<sub>1</sub> decreased by  $\geq 20\%$ , whereas on study days 2 and 3, the calculated PD<sub>20</sub> was administered. Since FEV<sub>1</sub> decreased by  $\geq 30\%$  after the last allergen dose on the qualifying day in subjects 1, 3, and 4, the PD<sub>20</sub> dose on the study days represented a lower dose of allergen.

the late phase, whereas placebo was markedly more effective than gallopamil in subject No. 4 (Fig. 1). Both of these subjects required nebulized albuterol for relief of symptoms during the late phase of the corresponding, less effective, regimen.

On study days with allergen challenge, the GM baseline histamine PC<sub>20</sub> was 6.2 mg/ml before placebo treatment and 5.7 mg/ml before gallopamil treatment (Table III). A histamine challenge could not be performed at 24 hours in three subjects after gallopamil treatment and in one subject after placebo treatment because of persistent bronchospasm (FEV<sub>1</sub>  $\leq 65\%$  predicted). However, in those subjects in whom PC<sub>20</sub> could be measured, the value at 24 hours was lower than the PC<sub>20</sub> before allergen in all but one subject (Table III). If inhaled albuterol was required during the night, the histamine challenge was delayed until 6 hours after drug administration. None of the subjects able to perform the histamine challenge at 24 hours received prednisone.

When histamine challenges were performed on study days 4 and 5, when no allergen was administered, gallopamil modestly attenuated basal airway responsiveness to histamine (Fig. 2). The GM  $\pm$

GSD fold increase in PC<sub>20</sub>  $\left( \frac{\text{PC}_{20} \text{ after}}{\text{PC}_{20} \text{ before}} \right)$  was

1.0  $\pm$  1.4 after placebo administration compared to 2.3  $\pm$  1.3 after gallopamil administration ( $p < 0.05$ ).

### DISCUSSION

This study is the first examining the effects of a calcium channel blocker on the LPR to inhaled allergen

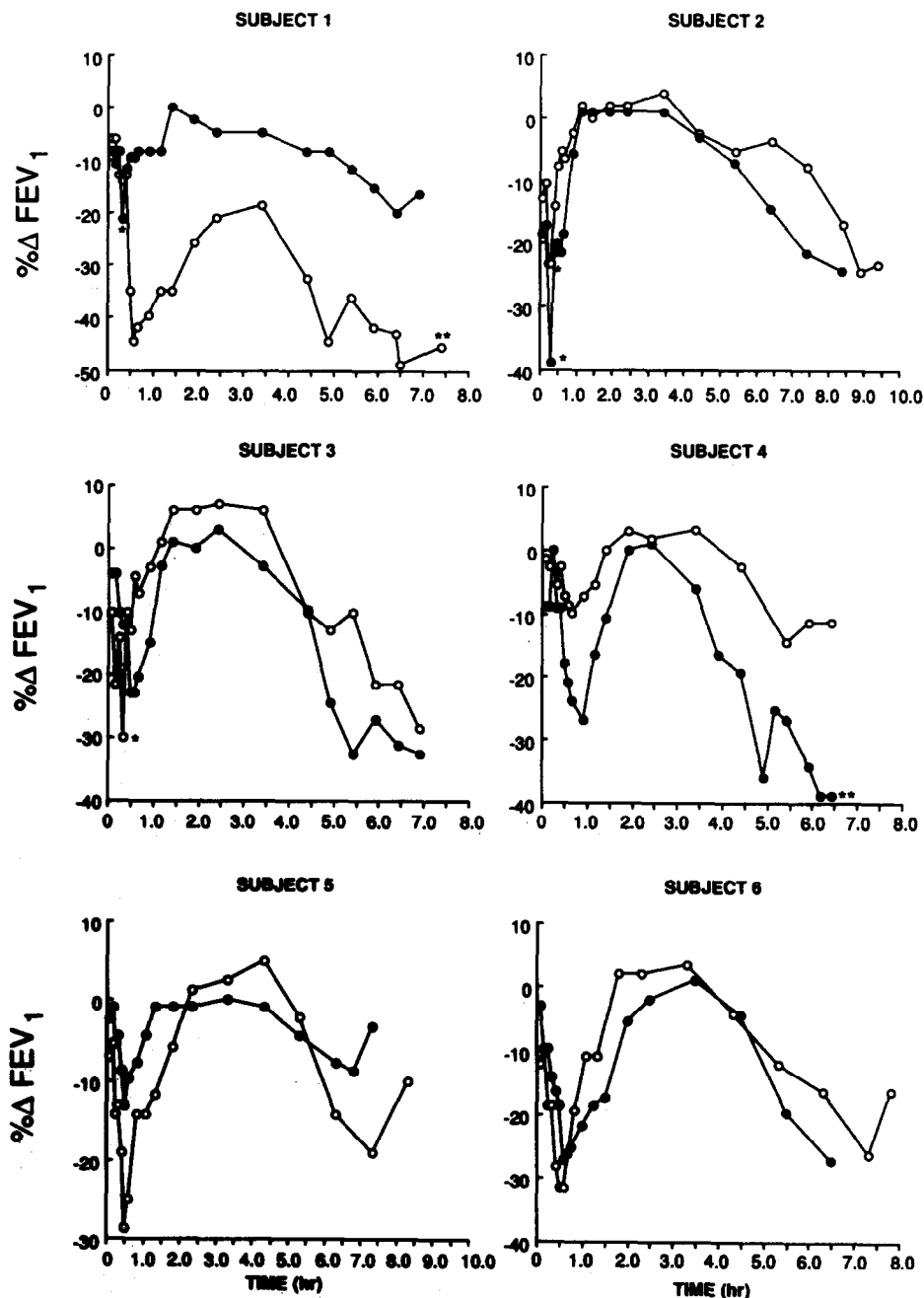


FIG. 1. Percent change in FEV<sub>1</sub> from postdiluent values during 8- to 10-hour period after inhaled allergen in each of six subjects. Subjects received inhaled gallopamil (●) or placebo (○) 30 minutes before allergen challenge. Subjects 1, 2, and 3 required isoproterenol to complete allergen challenge (\*), whereas subjects 1 and 4 required nebulized albuterol for relief of symptoms during late phase (\*\*).

in subjects with allergic asthma. Our results indicate that gallopamil administration did not attenuate the LPR. There was only a 21% chance of missing a 50% difference in maximum decrease in FEV<sub>1</sub> between active drug and placebo; >50% differences between active drug and placebo have been reported for cro-

molyn and inhaled beclomethasone.<sup>22</sup> In addition, gallopamil did not appear to prevent the allergen-induced increase in airway reactivity to histamine. In fact, fewer subjects were able to perform the histamine challenge at 24 hours after gallopamil than after placebo treatment because of persistent bronchoconstric-

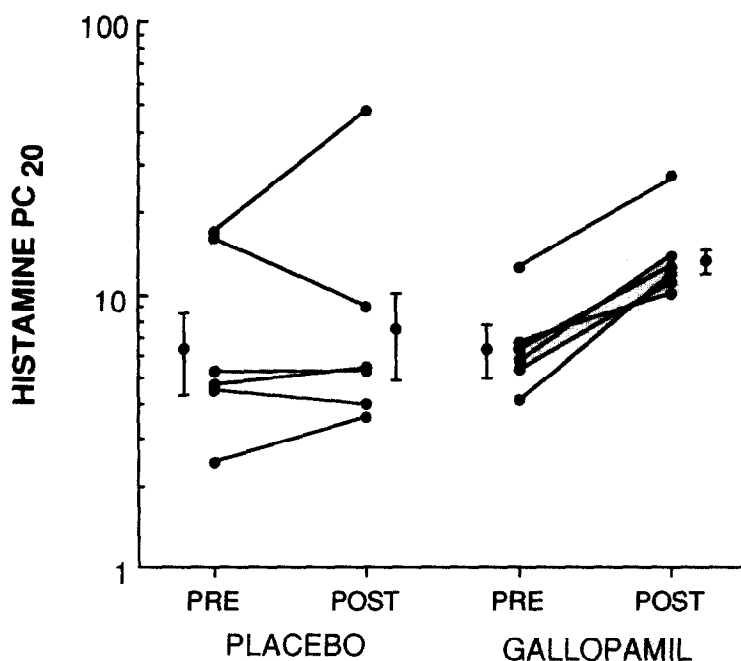


FIG. 2. PC<sub>20</sub> in each subject 1 hour before and 30 minutes after placebo treatment or inhaled gallopamil on study days 4 and 5 when no allergen was administered. GM  $\pm$  GSD PC<sub>20</sub> was  $6.4 \pm 2.1$  mg/ml before and  $7.5 \pm 2.6$  mg/ml after placebo treatment and  $6.4 \pm 1.4$  mg/ml before and  $13.3 \pm 1.4$  mg/ml after gallopamil treatment ( $p < 0.05$  for comparison with gallopamil pretreatment).

TABLE III. Airway reactivity to histamine before and 24 hours after allergen challenge

| Subject No. | Placebo                                  |                                               | Gallopamil                                    |                                               |
|-------------|------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
|             | PC <sub>20</sub> before allergen (mg/ml) | PC <sub>20</sub> 24 hr after allergen (mg/ml) | PC <sub>20</sub> 24 hr after allergen (mg/ml) | PC <sub>20</sub> 24 hr after allergen (mg/ml) |
| 1           | 8.0                                      | 0.6                                           | 3.0                                           | *                                             |
| 2           | 3.1                                      | *                                             | 3.2                                           | *                                             |
| 3           | 3.8                                      | 2.7                                           | 4.2                                           | 4.7                                           |
| 4           | 6.8                                      | 2.1                                           | 4.4                                           | *                                             |
| 5           | 9.0                                      | 8.5                                           | 16.0                                          | 4.4                                           |
| 6           | 10.0                                     | 7.9                                           | 12.0                                          | 4.6                                           |
| GM          | 6.2                                      |                                               | 5.7                                           |                                               |
| GSD         | 1.6                                      |                                               | 2.0                                           |                                               |

\*For safety, histamine challenges were not performed in subjects with persistent bronchospasm ( $FEV_1 < 65\%$  predicted).

tion. In contrast, the same dose and route of administration of gallopamil delivered a sufficient amount of drug to the lungs to attenuate basal airway responsiveness to histamine on a subsequent study day when no allergen was administered. Since the GM histamine PC<sub>20</sub> after placebo was not significantly different from the GM PC<sub>20</sub> measured before placebo administration, it is unlikely that the mean 2.3-fold increase in PC<sub>20</sub>

after gallopamil administration was a result of tachyphylaxis to histamine, as has been suggested by other investigators.<sup>26</sup> Moreover, in previous experiments in our laboratory, the mean fold increase in PC<sub>20</sub> was 0.93 (range, 0.8 to 1.1) when two histamine challenges were performed in 10 subjects on the same day 1½ hours apart, 1 hour before and 30 minutes after placebo administration. Thus, these data suggest that

calcium influx through the voltage-dependent channel does not play an important role in allergen-induced bronchoconstriction.

Our results differ from results of D'Brot et al.<sup>5</sup> who reported that gallopamil administration completely blocked the LPR to allergen in allergic sheep. The lack of effect of gallopamil on the late phase in the present study may be due to the short duration of action of this drug.<sup>12, 13</sup> However, cromolyn also has a short duration of protection against exercise-induced bronchoconstriction,<sup>27</sup> and yet it attenuates the LPR to allergen.<sup>22</sup> Therefore, it appears that gallopamil does not alter the inflammatory component of allergic asthma in humans.

Although in this study the magnitude of decrease in FEV<sub>1</sub> during the early phase was affected by isoproterenol administration, equal numbers of gallopamil- and placebo-treated subjects received this intervention. Even in the presence of gallopamil, two subjects still required isoproterenol, indicating that the drug was not providing adequate protection. The magnitude of decrease in the early phase did not appear to be affected by gallopamil administration. This contrasts with a study by Ahmed et al.<sup>14</sup> in which nebulized gallopamil (10 mg) provided significant protection against the early phase decrease in SG<sub>aw</sub>. The reasons for the discrepancy between their results and our results are unclear. The amount of drug reaching the lungs is likely to have been greater in our study because we gave twice the dose with similar particle size and nebulizer output. Moreover, this dose and method of administration, significantly, but modestly, decreased airway reactivity to histamine in the current study and to methacholine and exercise in previous studies from our laboratory.<sup>11-13</sup> However, our study differed from the study published by Ahmed et al.<sup>5</sup> in subject selection, method of measuring lung function, and allergen-administration technique. Our subjects were challenged with various allergens, based on history and skin testing, whereas all the subjects in the study by Ahmed et al.<sup>5</sup> were challenged with ragweed. We administered the same dose of allergen at each challenge and measured FEV<sub>1</sub> response, whereas Ahmed et al.<sup>5</sup> titrated the allergen dose required to produce a 35% decrease in SG<sub>aw</sub> during the early phase with each challenge. The major difference probably relates to their use of SG<sub>aw</sub> rather than FEV<sub>1</sub>, during allergen challenge. SG<sub>aw</sub> is so sensitive a measure that inhaled albuterol will produce increases suggestive of bronchodilation, even in the airways of healthy volunteers without asthma.<sup>28</sup>

In conclusion, inhaled gallopamil in maximum tolerated doses does not attenuate the LPR and probably does not alter the subsequent development of increased

airway hyperreactivity, after allergen. Since gallopamil is one of the most potent calcium channel blockers, when it is administered by the inhaled route, it is unlikely that this pharmacologic class of drugs will be clinically useful for the prevention of symptoms of allergic asthma.

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## REFERENCES

1. Lee VY, Hughes JM, Seale JP, Temple DM. Verapamil inhibits mediator release from human lung in vitro. *Thorax* 1983;38:386-7.
2. Jakschik BA, Sun FF, Lee L, Steinhoff MM. Calcium stimulation of a novel lipoxygenase. *Biochem Biophys Res Commun* 1980;95:103-10.
3. Pennington JE, Kemmerich B, Kazanjian PH, Marsh JD, Boerth LW. Verapamil impairs human neutrophil chemotaxis by a noncalcium-mediated mechanism. *J Lab Clin Med* 1986;108:44-52.
4. Russi EW, Marchette B, Yerger L, Abraham WM, Ahmed T. Modification of allergic bronchoconstriction by a calcium antagonist: mode of action. *Am Rev Respir Dis* 1983;127:675-9.
5. D'Brot J, Carpenter N, Abraham W, Ahmed T. Effect of gallopamil, a calcium channel blocker, on antigen-induced early and late bronchoconstriction in allergic sheep [Abstract]. *Am Rev Respir Dis* 1987;135:A312.
6. So SY, Lam WK, Yu DY. Effect of calcium antagonists on allergen-induced asthma. *Clin Allergy* 1982;12:595-600.
7. Russi EW, Danta I, Ahmed T. Comparative modification of antigen-induced bronchoconstriction by the calcium antagonists, nifedipine and verapamil. *Chest* 1985;88:74-8.
8. Ahmed T, Russi E, Kim CS, Danta I. Comparative effects of oral and inhaled verapamil on antigen-induced bronchoconstriction. *Chest* 1985;88:176-80.
9. Carpenter N, D'Brot J, Kim CS, Abraham WM, Ahmed T. Effect of gallopamil, a calcium channel blocker, on carbachol- and histamine-induced bronchoconstriction in sheep. *J ALLERGY CLIN IMMUNOL* 1988;81:859-66.
10. Patel KR, Tullett WM. Comparison of two calcium antagonists, verapamil and gallopamil (D600), in exercise-induced asthma. *Eur J Respir Dis* 1985;67:269-71.
11. Massey KL, Hill M, Harman E, Rutledge DR, Ahrens R, Hendeles L. Dose response of inhaled gallopamil (D600), a calcium channel blocker, in attenuating airway reactivity to methacholine and exercise. *J ALLERGY CLIN IMMUNOL* 1988;81:912-8.
12. Massey KL, Harman E, Hendeles L. Duration of effect of gallopamil, a calcium channel blocker, on methacholine-induced bronchoconstriction. *Pharmacotherapy* 1988;8:189-92.
13. Massey KL, Harman E, Hendeles L. Duration of protection of calcium channel blockers against exercise-induced bronchospasm: comparison of oral diltiazem and inhaled gallopamil. *Eur J Clin Pharmacol* 1988;34:555-9.
14. Ahmed T, Kim CS, Danta I. Inhibition of antigen-induced bronchoconstriction by a new calcium antagonist, gallopamil: comparison with cromolyn sodium. *J ALLERGY CLIN IMMUNOL* 1988;81:852-8.
15. Cockcroft DW. Mechanism of perennial allergic asthma. *Lancet* 1983;2:253-6.

16. Morris JF, Koski A, Johnson LC. Spirometric standards for healthy nonsmoking adults. *Am Rev Respir Dis* 1971;103:57-67.
17. Ahrens RC, Harris JB, Milavetz G, Annis L, Ries R. Use of bronchial provocation with histamine to compare the pharmacodynamics of inhaled albuterol and metaproterenol in patients with asthma. *J ALLERGY CLIN IMMUNOL* 1987;79:876-82.
18. McCubbin M, Ahrens R, Annis L, Vander Meulen J. Pharmacodynamics and pharmacokinetics of inhaled terbutaline (T) in asthmatic subjects [Abstracts]. *Am Rev Respir Dis* 1987;135:229.
19. Walker SB, Bierman CW, Pierson WE, Shapiro GG, Furukawa CT, Mingo TS. Bitolterol mesylate in exercise-induced asthma. *J ALLERGY CLIN IMMUNOL* 1986;77:32-6.
20. American Thoracic Society Subcommittee on Bronchial Inhalation Challenges, Assembly of Allergy and Clinical Immunology. Guidelines for bronchial inhalation challenges with pharmacologic and antigenic agents. *ATS News Spring* 1980:11-9.
21. Cockcroft DW, Murdock KY, Kirby J, Hargreave F. Prediction of airway responsiveness to allergen from skin sensitivity to allergen and airway responsiveness to histamine. *Am Rev Respir Dis* 1987;135:264-7.
22. Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses, and increased bronchial responsiveness to histamine. *J ALLERGY CLIN IMMUNOL* 1987;79:734-40.
23. Lai CKW, Twentyman OP, Holgate ST. The effect of an increase in inhaled allergen dose after rimeterol hydrobromide on the occurrence and magnitude of the late asthmatic response and the associated change in nonspecific bronchial responsiveness. *Am Rev Respir Dis* 1989;140:917-23.
24. Parks DP, Ahrens RC, Weinberger MM. Histamine challenges repeated at 1½-2 hours do not induce tachyphylaxis [Abstract]. *Am Rev Respir Dis* 1989;139:590.
25. Marks RG. Analyzing research data: the basics of biomedical research methodology. Belmont, Calif.: Lifetime Learning Publications, 1982:43-4, 61-4.
26. Manning PJ, O'Byrne PM. Histamine bronchoconstriction reduces airway responsiveness in asthmatic subjects. *Am Rev Respir Dis* 1988;137:1323-5.
27. König P, Hordvik NL, Kreutz C. The preventive effect and duration of action of nedocromil sodium and cromolyn sodium on exercise-induced asthma (EIA) in adults. *J ALLERGY CLIN IMMUNOL* 1987;79:64-8.
28. Holgate ST, Baldwin CJ, Tattersfield AE. Beta-adrenergic agonist resistance in normal human airways. *Lancet* 1977;2:375-7.

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