# Role of Calcium Channel Blockers in Longterm Treatment of Asthma

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## A. Introduction

The pathologic events underlying most cases of asthma are chronic inflammation of the airway walls and bronchoconstriction, both ocurring secondary to immediate and delayed release of mediators triggered by contact with allergens, exercise, cold air, smoking and occupational exposure.' Given the evidence that asthma is an inflammatory disease, it is logical for management to focus on blocking the many mediators of the response. Successful treatment options include combinations of corticosteroids, cromolyn sodium, theophylline, leukotriene antagonists and B2 agonists; each addressing different aspect of inflammation. Although these options have been shown to decrease asthma symptoms and as many new agents appear to have clinical benefit, i.e.immunotherapy; asthma continues to be a disease with significant morbidity-as evidenced in many US emergency rooms.[1]

Calcium ions play an important role in asthma. Calcium is involved in excitationcontraction of bronchial smooth muscle and also in secretory processes including the release of mast cell mediators which cause inflammation and bronchoconstriction. Calcium channel blockers are known to have many uses in cardiovascular disease and has often used to safely treat hypertension in asthmatics.[2] In vitro studies have shown CCB were also was a potent ariway relaxants, canine bronchial smooth muscle has shown Ttype Ca channels to play a central role in smaller airways in addition to the known L-type Ca current.[3]

Clinical trials however have yielded mixed results leading to a lack of information about calcium channel blockers in the recent past. Several studies have shown benefit of nifedipine in exercise induced asthma, but failed to show any effect on resting bronchomotor tone.[4] Some studies have shown modification on bronchoconstriction induced by histamine, allergen and acetylcholine but just as many failed to find a difference in respiratory status. Most studies did not continue patients[5] maintenance medications such as corticosteroids, and measurements were taken after only one or two doses of the CCB. The Merences found may also be related to differences in expressing results, for example FEV I ratios vs amount of allergen required to produce decrease in FEV (expressed as PD) or calculating airway conductance. Also several different formulations of CCB were used such as inhaled solution, sublingual and oral forms adding to difficulty comparing results. Asthma is multifactorial and therefore best treated with multiple medications aimed at varying aspects of the inflammatory response. No study has examined the role of chronic use of CCB in conjunction with other maintenance medication over an extended period of time.

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[1] Mills, Thomas. Pauwels, Romain and Holgate, Stephen. Alle . (2d edition). St. Louis: Mosby; 2001, 17-35.

[2] Frew, Anthony and Plummeridge, MB. *Alternative agents in asthma.* Journal Allergy and Clinical Immunology. 108: 3-10, 200 1.

[3] Hiroshi, Tanaka et al. *Effects of Candesartan on Cough and Bronchial Hyperresponsiveness in Mildly to Moderately Hypertensive Palients with Symptomatic Asthma.* Circulation. 104:281-285,2001.

[4] JanssenLukeJ. *T-type and L-type Ca currents in canine bronchial s7nooth muscle: characterization andphysiological roles.* American Journal Physiology. 272(6):CI757-1765

[5] MasseyKL.Etal. *Dose response ofinhaledgallopamil in attenuating airway reactivity to* methacholine and exercise. Journal of Allergy Clinical Immunology. 81: 912-8.1988.

**B. Review of Literature**

Moscato, Gianna, et al. *Effect of nifedpine on hyperreactive bronchial responses to methacholine.* Annals of Allergy. 56: 145-149, 1986.

Nine patients with occupational asthma randomized trial evaluating nifedipine, 20mg sublingually and bronchial reactivity to methacholine. Provocation dose of methacholine induced a 15% decrease in FEV expressed as PD I 5FEVI which on average increased from 3 1 Oug (SD 19 1) to 10 12 ug (SD640) P<. 0 1.

Patel, Kanti and Peers, Elizabeth. *Felodipine, a new calcium antagonist modifies exercise inducedasmtha.* American Review Respiratory Disease. 138: 54-58, 1988.

Double-blind, randomized crossover trial in 9 patients. Patients receiving steroids, theophylline, anticholinergic drugs were excluded. 10mg felodipine was compared to placebo; patients exercised 30 minutes after treatment and FEVI recorded for an hour after exercise. Results showed no effect on resting lung function but a statistically significant change in FEV I after exercise. FEV % change after exercise with placebo was 27 (4.5%) and 13.5% (3.7) after felodipine administration.

Russi, Erich. Et al. *Comparative modification of antigen-induced bronchoconstriction by the calcium antagonists, nifedpine and verapamil.* Chest. 88(l): 74-78. 1985

Twelve subjects received a single oral dose of nifedipine 20mg or verapamill60mg of verapamil before inhalation with ragweed antigen. Results were measure in mean specific airway conductance (Raw). Nifedipine protected against antigen induced bronchoconstriction in 67% (8/12) while verapamil protected in only 2/12 subjects.

So, SY, Lain, W.K. and Yu, D.C. *Effect of calcium antagonists on allergen-induced asthma.* Clinical Allergy. 12(595-600) 1982.

Eight allergic asthmatics were treated with inhaled verapamil 2.4mg and SL nifedipine before bronchial provocation using a common allergy. Niether drug changed the dose of allergen required to cause a 20% fall in FEV 1. Percent change in FEV I compared to control was 4.55 in Nifedipine group and 0.98 in Verapamil.

Harman, Eloise et al. *7he effect of oral difitiazem on Airway Reactivity to Methacholine and exercise in subjects with mild intermittent asthma.*

Single blind crossover study of 10 patients evaluation effect of increasing doses of oral dilitiazem on airway reactivity tested with exercise and methacholine challenge. No difference in dose of methacholine required to produce 20% drop in FEV I with placebo and with dilitiazem 60-180 mg.

Hoppe, Michael; Harman, Eloise; Hendeles, Leslie. Me *effect gallopamil, apotent calcium channel blocker, on the late-phase response in subjects with allergic asthma.*

Double blind randomized crossover trail in six patients. Subjects received 20 mg of inhaled gallopamil or placebo before challenge with same dose of allergen. During late phase maxurnum decrease in FEVI was 26.9% SDI 1.9 and 25.3% SD 10.3 with gallopamil p>0.05. Gallopamil did not significantly attenuate response to allergen. 3 patient required isoproterenol during the study.

**Hypothesis**

Do calcium channel blockers play a beneficial role in the longterm management of chronic asthma in conjunction with other medications?

**Methods Outcomes**

1.Principal outcome is change in FEVI% after methacholine bronchial provocation over 6months. FEVI will be measured with spirometry and methacholine solution is titrated until there is a decrease of FEVI of 20% at baseline upon inhalation. Patient will undergo a two week observation period, measuring AM peak flow rate and rate symptoms before undergoing intervention, placebo vs nifedipine 20mg long acting. Nifedipine (long acting) chosen at this dose per benefit in prior studies used in oral form. This dose has also been safely used as control for assessment of antihypertensives. Measure response of FEV to methacholine weekly for four weeks recorded and then every month to monitor changes in FEVI % .

2. Change in symptoms evaluated by questionaire at weekly visits. Monitor increassed use of albuterol, nocturnal symptoms, chest tightness, dyspnea on exertion. Follow for complications such as hospitalizations, ER visits. Patients will bring maintenance medications each visit to assess compliance.

3. Secondary outcome effect of CCB on cardiovascular system At visits follow blood pressure and change in activity level, follow baseline EKG and at end of study.

**C. Study Design**

Longitudinal prospective double blinded clinical trial, randomized to nifedipine or placebo Measure subjects baseline FEV and methacholine provocation dose after two week observation period when peak flow is measured QAM. Baseline and study measurements will taken as mean of three measurements of FEVI% at each visit. Patients will continue on home asthma medications such as corticosteroids, Bagonist, leukotriene antagonist; patients must not have medication dosage changed while in study unless symptomatic and requiring treatment. We will follow use of short acting albuterol which patients may use as needed. They will be followed for six months and seen weekly for evaluation of symptoms and blood pressure. Spirometry to evaluated initially every week for 4 weeks and then at 4 week intervals. Every month methacholine provocation will be performed given patients FEV I that day is within 10% of baseline and 65% of predicted for age sex and height.

**D. Statistical AnaLlsis**

**T test:** compare percent change in FEV

Baseline change approximately 27% with methacholine challenge

Power calculation: n= 1 + 16 (stand-devn/effect)$^2$ Assumed 7% effect difference would be significant (studies have shown 0-20%), 80% power and alphaO.05

Estimated sample size: 40 subjects in each group

**E. Inclusion Criteria**

- Select adult asthmatic patients from adult AIM clinic as diagnosed by use of the American Thoracic Society criteria for bronchial asthma: may include classifiction from mild intermittent to severe persistent but without recent hospitalization in past 4 weeks.
- Treated with effective management: steroids, B agonist, leukotriene inhibitor with best FEVI at least more than 65% predicted

**F. Exclusion Criteria**

No recent (4 week history) of URI, hospitalization or allergic symptoms
Coronary artery disease or anginal symptoms
Hypotension (SBP< 100)
History of arrythmia
Cannot be taking another CCB for cardiovascular disease

Informed consent in both English and Spanish given clinic population

Risk: If patients develop an increase in symptoms requiring hospitalization-intervention will be held.

Drug side effects: hypotension, headaches, acid reflux, arrythmiast.