

Effect of angiotensin II receptor blockade on bronchial responsiveness in asthmatic subjects

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The peptide hormone angiotensin II (A II) stimulates a variety of physiologic responses that support arterial blood pressure and, in addition, may contribute to the pathogenesis of hypertension, vascular disease, heart failure, and diabetic nephropathy.¹ The A II type-1 receptor antagonists constitute a new class of drugs designed to competitively displace A II from its type-1 receptor subtype. Losartan was the first A II type-1 receptor antagonist to receive approval in the United States as an antihypertensive agent.

Plasma A II levels have been shown to be elevated during acute exacerbations of asthma.² Furthermore, intravenous infusion of A II into stable asthmatic subjects enhances bronchial responsiveness to inhaled methacholine.³ Because therapy with A II receptor antagonists causes elevation of plasma A II levels,⁴ a theoretical basis exists for A II blocker-induced enhancement of bronchial responsiveness in asthmatic subjects. In support of this theory, we have recently reported the occurrence of bronchospasm in 3 pharmacists with stable asthma who were exposed to pulverized losartan.⁵ To further investigate the influence of A II receptor blockade on airway reactivity, we performed a randomized, double-blind, placebo-controlled, crossover study evaluating the effect of a 1-week course of oral losartan on bronchial responsiveness to inhaled methacholine in a group of subjects with mild, stable asthma.

METHODS

Subjects

Ten asthmatic volunteers (3 men, 7 women; age range, 19 to 48 years) granted informed consent and participated in the study, which was approved by our hospital's institutional review board. Subjects were asymptomatic and had not experienced asthma exacerbations or symptoms of upper respiratory tract infection or seasonal allergies for at least 4 weeks before enrollment. None of the subjects had used oral or inhaled steroids for at least 6 weeks before participation in the study. All subjects used inhaled albuterol on an as-needed basis as their sole antiasthmatic medication.

Abbreviations used

A II:	Angiotensin II
FVC:	Forced vital capacity

Study protocol

All subjects demonstrated baseline hyperresponsiveness to inhaled methacholine, defined as a PC_{20} of less than 8 mg/mL. Subjects were randomly assigned to receive losartan (Cozaar; Merck & Co, West Point, Pa) 50 mg once daily for 7 days or identical placebo, after which bronchoprovocation challenge was repeated. After a 1-week washout period, subjects crossed over to the alternate treatment arm, with methacholine challenge testing before and after the 7-day course of therapy. Subjects abstained from albuterol for at least 18 hours before each study. A week-long course of therapy was chosen because the antihypertensive effect of losartan is significantly greater after 7 daily doses than after the first dose.⁶

Bronchial challenge studies

After performing baseline spirometry, subjects inhaled 5 breaths from functional residual capacity to total lung capacity of physiologic saline followed by progressively increasing concentrations of methacholine (Provacholine; Roche Laboratories, Nutley, NJ) administered by means of a nebulizer (model 646; DeVilbiss Health Care Inc, Somerset, Pa) controlled by a dosimeter (KoKo DigiDoser; Pulmonary Data Service Instrumentation Inc, Louisville, Colo). The study was terminated when a greater than 20% decrement in postsaline FEV_1 was induced. PC_{20} was determined by interpolation from a log dose-response curve.

All bronchial challenge studies were performed at approximately the same time of day for each subject. Posttherapy studies were initiated 2 hours after ingestion of the seventh dose of study drug to correlate with maximal plasma levels of losartan.⁶

RESULTS

Mean (SEM) age of the 10 subjects was 31.0 (2.7) years. Mean values for log PC_{20} , forced vital capacity (FVC), and FEV_1 are given in Table I. The 7-day course of losartan did not significantly affect bronchial responsiveness for the group as a whole. Two subjects demonstrated a greater than 50% reduction in baseline PC_{20} after administration of losartan, as did 3 subjects after administration of placebo (Fig 1).

Small but statistically significant decrements in FVC and FEV_1 were demonstrated after the 7-day course of losartan, although postlosartan and postplacebo values were not significantly different. No respiratory symptoms or other adverse reactions were reported by any study subject.

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TABLE I. Effects of 1-week course of oral losartan

	Losartan			Placebo		
	Before	After	P value	Before	After	P value
log PC ₂₀	-0.094 (0.16)	-0.20 (0.14)	NS	-0.223 (0.16)	-0.35 (0.19)	NS
FVC (L)	3.61 (0.23)	3.45 (0.22)	.03	3.47 (0.27)	3.44 (0.26)	NS
FEV ₁ (L)	2.75 (0.20)	2.63 (0.20)	.008	2.64 (0.22)	2.63 (0.21)	NS

All values expressed as mean (SEM).

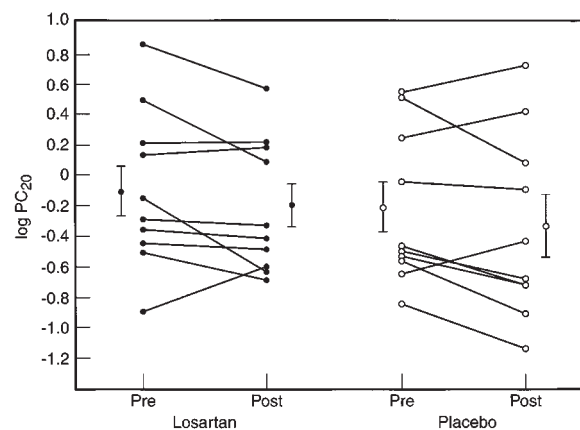


FIG 1. Effect of 7-day course of losartan (50 mg daily) and placebo on bronchial responsiveness to methacholine. Changes were not statistically significant. PC₂₀, Concentration (mg/mL) of methacholine inducing 20% decline in FEV₁ from postsaline baseline. Error bars indicate $\pm$ SEM.

DISCUSSION

This study has failed to demonstrate a significant effect of a 7-day course of oral losartan (50 mg daily) on bronchial responsiveness to inhaled methacholine in a group of stable asthmatic subjects. Because therapy with A II receptor antagonists causes elevated plasma A II levels,⁴ and intravenous A II infusion enhances methacholine responsiveness in subjects with stable asthma,³ our negative results may be explained by the inability of losartan, administered at the recommended therapeutic dosage, to sufficiently elevate plasma or pulmonary tissue levels of A II so as to enhance bronchial responsiveness. These

results, however, cannot necessarily be extrapolated to patients with more severe asthma or to any asthmatic patient during an exacerbation of their illness.

Our observation of a small but statistically significant decrement in FEV₁ and FVC after losartan is unexpected in light of previous work. Studies of intravenous A II infusion in subjects with mild asthma have demonstrated no effect on FEV₁ at levels inducing a significant increase in bronchial responsiveness to methacholine.³ Given that postlosartan and postplacebo FEV₁ and FVC values in our study group were nearly identical (Table I), our results may merely reflect inherent variability in spirometric values among a relatively small group of asthmatic subjects.

In summary, therapy with the A II receptor antagonist losartan, at recommended dosages, does not enhance bronchial responsiveness in subjects with mild, stable asthma.

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