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Losartan-induced bronchospasm

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Losartan is the first angiotensin II type 1 (AT₁) receptor antagonist to become available for the treatment of hypertension. Because the mechanism of action of the AT₁ receptor antagonists does not involve the inhibition of angiotensin-converting enzyme (ACE), side effects induced by ACE inhibitors are not expected to occur with these agents. Adverse effects of ACE inhibition include cough¹ and (rarely) bronchospasm² and angioedema,¹ probably caused by the protussive and bronchoconstricting agents bradykinin and substance P, which are normally degraded by ACE and therefore accumulate when the enzyme is inhibited. However, two reported cases of losartan-induced angioedema³ suggest that the AT₁ receptor antagonists may not be entirely free of ACE inhibitor-related side effects.

We herein describe the development of upper airway discomfort and bronchospasm in three hospital pharmacists who inadvertently inhaled losartan in the course of preparing capsules containing the drug.

CASE REPORTS

Three of four pharmacists at our hospital pharmacy experienced acute onset of respiratory symptoms including throat discomfort, nasal irritation, chest tightness, and cough while preparing capsules containing losartan for use in a blinded, placebo-controlled study. The pharmacists' task included pulverizing, with mortar and pestle, 50 tablets, each containing 50 mg of losartan (Cozaar; Merck & Co., West Point, Pa.), into a fine

Abbreviations used

ACE: Angiotensin-converting enzyme
AT₁: Angiotensin II type 1

powder and subsequently transferring 50 mg of powder into capsules.

Symptoms were noted almost immediately on initiation of crushing of the tablets and persisted for several hours. All episodes occurred during the subjects' initial exposure to the drug. Each of the pharmacists who experienced symptoms had previously engaged in similar projects involving other medications without having any reaction. All three individuals reported histories of mild asthma but were free of symptoms and had not required any medication for treatment of respiratory symptoms in the previous 4 to 10 months.

Study methods

To objectively evaluate the effect of losartan exposure, we performed a double-blind, placebo-controlled, crossover study, for which subjects granted informed consent. On two separate days, each pharmacist underwent spirometry (performed by a blinded pulmonologist) before and after exposure to losartan or placebo. While blindfolded, subjects pulverized 50 losartan tablets (50 mg each) or placebo for exactly 5 minutes in a manner identical to that of their initial exposure. For the placebo studies, we used a combination of ranitidine hydrochloride and sertraline hydrochloride tablets, which were indistinguishable from the study drug to the blinded participants and which contained the two types of dye (D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake) present in the film coating of the losartan tablets.

On a separate day, allergy skin testing was performed on two of the subjects. A 50 mg losartan tablet was dissolved in 5 ml of sterile albumin saline solution with phenol (Bayer, Spokane, Wash.) to produce a 10 mg/ml solution, which was used to perform a percutaneous skin

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TABLE I. Effects of losartan exposure

Subject No.	ΔFEV_1 (%)		Symptoms with losartan exposure		
	Placebo	Losartan	Nasal/throat irritation	Cough	Chest tightness
1	-2	-9	+	+	+
2	0	-19	+	+	+
3	+2	-11	+	+	-

ΔFEV_1 , Change in FEV₁ from baseline after inhalation challenge.

prick test on the volar aspect of an alcohol-prepped forearm in each subject. The solution was then filter-sterilized by using a 0.22 μ m filter (Millipore, Bedford, Mass.), and serial dilutions were made with the sterile albumin saline buffer. Intradermal skin tests were performed with incremental doses of losartan solution (0.01, 0.1, and 1.0 mg/ml) at 15-minute intervals until a positive result (>3 mm wheal or >5 mm flare) was obtained or until the maximal concentration was administered.

Several weeks later, one subject (subject 3) underwent bronchial provocation challenge with methacholine before and after administration of one and seven oral doses of losartan, taken as a 50 mg tablet once daily. During each study, five vital capacity breaths of incremental concentrations of methacholine were inhaled until a 20% decrease in FEV₁ occurred. The concentration (in milligrams per milliliter) of methacholine inducing this decrement (PC₂₀) was calculated by interpolation from a log dose-response curve.

RESULTS

All three subjects experienced symptoms within 2 minutes of exposure to inhaled losartan. Symptoms were identical to those experienced during the initial exposure, including nasal and throat irritation, chest tightness, and cough. During the placebo study, only a bitter taste was reported by each subject. The two preparations were not distinguishable by odor. Spirometry revealed that FEV₁ was decreased in each subject after exposure to losartan (Table I) but was only minimally affected by placebo. Because of the small sample size, this difference did not achieve statistical significance ($p = 0.064$ by two-tailed paired t test).

Results of percutaneous tests and all three intradermal skin tests were negative in each subject. No evidence of wheal or flare reaction was demonstrated.

A single dose of oral losartan (50 mg) had no effect on bronchial responsiveness in subject 3; however, after 7 days of therapy, while pulmonary function values remained stable, an increase in sensitivity to methacholine was demonstrated: PC₂₀ decreased from 3.99 mg/ml to 1.18 mg/ml.

DISCUSSION

We report the acute onset of upper respiratory tract symptoms and bronchoconstriction in three pharmacists who inhaled losartan in the course of pulverizing tablets containing the drug. All three subjects had previously performed similar tasks with numerous other medications without experiencing similar symptoms. It is highly unlikely that inactive ingredients are responsible for the observed effect, because losartan is combined with inert agents common to many other medications, namely, microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, and titanium dioxide.⁴ To exclude the possibility that the two dyes contained within the coating of the losartan tablet were the causative agents, placebo tablets, which contained these two identical substances and similar inert ingredients, were chosen.

The mechanism by which losartan induced bronchospasm in our subjects is unclear. Skin testing provided no evidence of an IgE-mediated reaction. The inhaled drug may have physiologic activity on airway smooth muscle causing nonspecific bronchial hyperresponsiveness. It is also possible that inhaled losartan interacts with AT₁ receptors within the respiratory tract. These receptors have been demonstrated in various human tissues⁵ including adrenal cortex, brain, kidney glomeruli, uterus, and placenta and in the rat lung.⁶ A recent study has demonstrated that angiotensin II potentiates methacholine-induced bronchoconstriction in isolated human bronchi, as well as in patients with mild asthma.⁷ Perhaps a modulation of airway levels of angiotensin II may explain the observed effect of inhaled (and, in one subject, systemic) losartan.

The clinical significance of these findings remains to be elucidated. It is noteworthy that all three subjects reported herein have a history of mild asthma, though they had all been free of symptoms for several months. Whether the use of oral losartan at recommended doses can result in significant bronchoconstriction remains to be seen as clinical experience with the drug increases.

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Computed tomographic study of the paranasal sinuses in allergic rhinitis

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In recent years, there has been much interest in the relationship between allergic rhinitis and sinusitis. One aspect of sinus disease that still remains undefined is the role of allergic inflammation on the sinus mucosa. Clinically, patients can report congestion and discomfort localized to the sinuses during periods of symptomatic allergic rhinitis. Our group previously reported that inflammation of the sinuses could be detected on single photon emission computerized tomography in pure allergic rhinitis.¹ The ability to demonstrate allergic sinusitis with computed tomographic (CT) scans during periods of symptomatic allergic rhinitis would have important therapeutic implications. A recent study demonstrated a number of significant changes in the sinus cavities on CT scan in patients with viral upper respiratory tract infections.² To determine whether allergic rhinitis results in sinus inflammation that could be detected by CT scan, we studied adults by using limited CT scans during episodes of symptomatic allergic rhinitis.

METHODS

Limited coronal CT scans of the nasal passages, osteomeatal complex, and paranasal sinuses were ob-

Abbreviation used

CT: Computed tomographic

tained for nine atopic subjects before the pollen seasons and when subjects were experiencing symptoms during documented pollen seasons. Subjects were enrolled during successive ragweed and tree or grass pollen seasons in St. Louis between 1994 and 1996. Patients were determined to be allergic by history, physical examination, and allergy skin testing. All CT scans were read in a blinded fashion by a radiologist. All participants signed an informed consent statement, which had been approved by the institutional review board.

RESULTS

During the pollen season, all nine patients had symptoms of allergic rhinitis including sneezing, nasal pruritus, rhinorrhea, and nasal congestion. All had markedly swollen, pale nasal turbinates on physical examination. None demonstrated any clinical symptoms of sinusitis. There were several minor incidental findings noted on preseasonal baseline CT scans. One patient had a small (1 mm) maxillary retention cyst, which remained unchanged as shown on the seasonal CT scan. Another patient had paradoxical turbinates. Septal deviation was identified in five of nine subjects.

In six of nine subjects (67%), both the pre-seasonal and seasonal CT scans demonstrated normal osteomeatal complex and normal lining of the paranasal sinus mucosa. The seasonal CT scans

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