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INCIDENCE OF COUGH INDUCED BY IMIDAPRIL IN PATIENTS WITH HYPERTENSION WITH ENALAPRIL-ASSOCIATED COUGH

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ABSTRACT

The purpose of this study was to determine the incidence of cough and changes in blood levels of prostaglandin after replacement with imidapril in patients with hypertension with a history of enalapril-induced cough. In 18 patients (3 men and 15 women), enalapril decreased mean aortic blood pressure statistically significantly from 124 ± 14 mm Hg to 104 ± 12 mm Hg. Enalapril had to be withdrawn because of the development of irritating dry cough during this therapy. After verifying that the cough had disappeared following withdrawal of enalapril, we began medication with imidapril 5 mg in 15 (83%) of the 18 patients (1 patient had gastrointestinal irritation and 2 were lost to follow-up), resulting in a statistically significant decrease in mean aortic blood pressure from 128 ± 16 mm Hg to 108 ± 10 mm Hg. The cough profile during imidapril therapy was compared with that during enalapril therapy. During the follow-up period (31 ± 13 weeks), 5 patients (group 1, mean age 61 ± 17 years; 5 women) had to stop taking imidapril because of irritating cough, 6 patients had no cough (group 2, mean age 63 ± 12 years; 1 man, 5 women), and 4 patients who had a dry cough less severe than that during enalapril therapy but that did not preclude their continuing use of imidapril (group 3, mean age 69 ± 12 years; 2 men, 2 women). Imidapril had no effect on the plasma concentration of either prostaglandin $F_{2\alpha}$ or thromboxane B_2 in any group, but the prostaglandin E_2 concentrations showed a statistically significant increase in groups 2 and 3. Sulindac, a prostaglandin synthesis inhibitor, was administered to 3 patients in group 1 and 2 patients in group 3 selected at random. Sulindac abolished the cough completely in 4 patients and was partially effective in 1 patient. Imidapril could be used in 67% (groups 2 and 3) of patients with enalapril-induced cough. We conclude that local, not systemic, activation of the prostaglandin cascade is responsible for the development of this side effect of angiotensin-converting enzyme (ACE) inhibitors. Although this was an uncontrolled, open-label study, our results provide a potential new treatment with imidapril for patients with hypertension when ACE inhibitors are indicated but cough develops with

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their use. *Key words:* angiotensin-converting enzyme inhibitor, cough, hypertension, enalapril, imidapril.

INTRODUCTION

Angiotensin-converting enzyme (ACE) inhibitors are a class of antihypertensive drugs that inhibit the renin-angiotensin system by dilating systemic vessels. This characteristic may explain the clinical benefits that most ACE inhibitors afford in improving the mortality rate in patients with congestive heart failure[1] and in decreasing left ventricular hypertrophy to a greater extent than any other hypotensive agent.[2] Despite their favorable effects on neurohormonal balance, however, ACE inhibitors are known to produce an important side effect of persistent dry cough, which is the most common reason for drug withdrawal.[3,4] The incidence of cough is variable according to the population, ranging from about 0.3% to 33%.[5,6] This wide range can be explained by several factors, including the methods used to detect cough,[7] the differences in observation periods, the types of ACE inhibitors, and the patient populations. Although cough apparently does not recur when captopril[8] or delapril[9] is substituted for enalapril, rechallenge with the same or another ACE inhibitor generally results in its recurrence,[3,10–15] and thus change to another ACE inhibitor is not recommended. Imidapril, recently released commercially in Japan, was found in a double-masked study to result in less incidence of cough (0.9%) compared with enalapril.[16]

The aim of this present study was to determine the incidence of cough and the correlation between systemic prostaglandin level and cough in patients with a history of enalapril-induced cough. Thus we administered imidapril to patients who had to be withdrawn from enalapril therapy because of irritating cough, and measured their blood concentrations of prostaglandin.

PATIENTS AND METHODS

Study Patients

This was an uncontrolled, open-label study that consisted of 18 patients (3 men and 15 women) 45 to 91 years of age. All had complained of irritating and annoying cough while receiving enalapril therapy for essential hypertension and had to be withdrawn from therapy because of this adverse effect. During enalapril therapy, the median time until the patients developed a confirmed cough was 6 weeks. Cough severity was evaluated by 3 doctors using a self-administered questionnaire. All patients included in this study had cough that disturbed their daily life, work efficiency, or night sleep. We excluded other patients who developed less

severe cough but could still continue enalapril therapy. Although it is difficult to establish a clear difference between severe and mild cough even with use of a questionnaire, we believe that the 15 patients who completed the present study represented a homogeneous group who had such severe and irritable cough that they could not and did not want to continue enalapril therapy. All patients had normal findings for chest roentgenograms and normal clinical laboratory evaluations in blood screening tests. We could not identify any abnormal condition or disease in any patient that would have been responsible for coughing. The patients returned to our outpatient clinic within 4 weeks after the withdrawal of enalapril, and all of them stated that their cough had stopped completely. Following this washout period, they started imidapril therapy. Imidapril was used as monotherapy in 16 of 18 patients, and the other 2 patients received a calcium channel blocker as combined therapy.

Study Methods

During the washout period following enalapril withdrawal, the blood concentrations of prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), and thromboxane B_2 (TXB_2) were measured by radioimmunoassay. Blood samples were immediately centrifuged, stored at a cool temperature, and analyzed on the same day. Normal values were as follows: PGE_2, <8.4 pg/mL; $PGF_{2\alpha}$, 55 to 292 pg/mL; and TXB_2, 14 to 50 pg/mL. Each patient was then given imidapril at an initial dose of 5 mg. The dose of imidapril was increased to 10 mg in one patient because of inadequate blood pressure control (systolic, >140 mm Hg, diastolic, >90 mm Hg). Blood pressure was measured at the upper arm with the patient in a sitting position after at least 30 minutes of rest and 1 hour later for any patient who smoked. We measured the blood concentrations of PGE_2, $PGF_{2\alpha}$, and TXB_2 again when the patient developed cough or at least 8 weeks after the beginning of imidapril therapy. In groups 1, 2, and 3, these repetitions were done at 10.5 ± 5, 11 ± 3, 13.5 ± 3 weeks, respectively (mean ± SD). Written informed consent was obtained from all patients after the study design and purpose were explained. Patients were not informed of the potential for less incidence of imidapril-induced cough to avoid the possibility of the occurrence of less coughing due to the psychological placebo effect of the information.

Sulindac (200 mg), a prostaglandin synthesis inhibitor, was administered to three patients in group 1 and two patients in group 3, selected at random. We did not administer sulindac to all patients because it was not included in the original study protocol. Patients selected were informed that this medication might be effective in reducing cough.

Statistical Analysis

The primary end point of this present study was the onset of dry cough during imidapril therapy. To estimate the proportion of patients who could switch from enalapril to imidapril for treatment of hypertension, we evaluated the cough profile during imidapril therapy with respect to the incidence, severity, and frequency of cough in comparison with the enalapril-induced cough, using a self-administered questionnaire with a 4-point rating scale as follows: 0 (no cough), 1 (better), 2 (same), and 3 (worse). All data are expressed as mean ± SD. Statistical analysis was performed using paired or unpaired Student's t test and Mann-Whitney statistic test, as appropriate. A P value < 0.05 was considered significant.

RESULTS

All patients in this study showed a significant decrease in mean aortic blood pressure during enalapril therapy (124 ± 14 mm Hg to 104 ± 12 mm Hg; $P < 0.05$). During the mean follow-up period of 31 ± 13 weeks after enalapril withdrawal, the mean aortic pressure was 108 ± 10 mm Hg, decreased from 128 ± 16 mm Hg ($P < 0.05$). During imidapril therapy, one patient had gastrointestinal irritation and two patients were lost to follow-up. The remaining 15 patients were assigned to three groups, as follows: group 1: 5 patients (mean age, 61 ± 17 years) with irritable cough that required them to discontinue imidapril (cough score = 2); group 2: 6 patients (mean age, 63 ± 12 years) who did not complain of cough during imidapril therapy (cough score = 0); and group 3: 4 patients (mean age, 69 ± 12 years) who had a less severe dry cough compared with that during enalapril therapy and could continue to use imidapril (cough score = 1). No patient had worse cough (cough score = 3) during imidapril therapy compared with cough during enalapril therapy. No other adverse effects were noted, except that one patient developed gastrointestinal irritation during 10 mg of imidapril therapy. The clinical characteristics of the patients in each group are shown in Table I. All of the patients in group 1 were women, and their cough disappeared within 1 week after imidapril withdrawal. Six patients in group 2 had no cough for a mean interval of 43 weeks. The incidence rate of withdrawal due to imidapril-induced cough was 33% (5 of 15) among those patients who had had irritable cough during enalapril therapy. Thus about 10 (67%) of 15 patients were able to switch from enalapril to imidapril.

No difference was observed among the three groups in the blood concentration of PGE_2, $PGF_{2\alpha}$, or TXB_2 during the washout periods before the imidapril therapy (Table II). Imidapril did not affect the blood concentra-

Table I. Clinical characteristics of study groups. Values are expressed as mean ± SD where indicated.

	Group 1 (n = 5)	Group 2 (n = 6)	Group 3 (n = 4)
Sex			
Male	0	1	2
Female	5	5	2
Age (y)	61 ± 17	63 ± 12	69 ± 12
Body weight (kg)	55 ± 7	59 ± 6	64 ± 3
Smokers (n)	0	1	2
Blood pressure (mm Hg)			
Baseline (systolic/diastolic)	170 ± 14/96 ± 11	156 ± 10/93 ± 7	161 ± 17/81 ± 16
During enalapril	137 ± 27/76 ± 11*	124 ± 18/80 ± 4*	133 ± 14/74 ± 16*
During imidapril	145 ± 24/81 ± 7*	117 ± 18/78 ± 10*	133 ± 13/72 ± 15*
Duration of hypertension (y)	4.2 ± 1.1	6.0 ± 2.4	5.5 ± 2.3
Time until onset of cough after drug treatment (wk)			
With enalapril	6.2 ± 7	5.2 ± 3	7.5 ± 4
With imidapril	8.0 ± 8	Continued	12.0 ± 9

* $P < 0.05$ versus baseline.

tion of either $PGF_{2\alpha}$ or TXB_2 in any group, but a significant increase in PGE_2 was seen in groups 2 and 3.

Four (80%) of the five patients receiving sulindac reported complete disappearance of cough after the sulindac treatment was begun, and the severity of cough was decreased in one patient in group 1. The mean aortic blood pressure did not change after sulindac administration.

DISCUSSION AND CONCLUSIONS

ACE inhibitor-associated cough has been consistently described as dry, nonproductive, and worse at night.[11,15] We observed the incidence of cough in these patients for a considerable period, because cough can develop

Table II. Blood levels (in picograms per milliliter) of prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), and thromboxane B_2 (TXB_2). Values are expressed as mean ± SD.

	Group 1	Group 2	Group 3
PGE_2			
During washout	1.7 ± 0.6	2.8 ± 2.0	2.6 ± 1.5
During imidapril	2.2 ± 0.7	4.4 ± 1.9*	5.1 ± 1.7*
$PGF_{2\alpha}$			
During washout	226 ± 34	217 ± 25	217 ± 50
During imidapril	207 ± 19	210 ± 29	220 ± 45
TXB_2			
During washout	31 ± 12	22 ± 17	16 ± 13
During imidapril	34 ± 14	21 ± 19	20 ± 15

* $P < 0.05$ versus during washout.

within the first week or have a delayed onset of up to 6 months after the start of therapy.

The mechanisms of ACE inhibitor-induced cough remain unclear. Kinins, one of the proinflammatory mediators normally degraded partly by ACE, accumulate in the lung as a result of inhibition of ACE, thus promoting cough and bronchospasm in susceptible persons.[17] This hypothesis is supported by the reports of the stimulation by bradykinin of afferent sensory C-fibers by type J receptors involved in the cough reflex,[18] the bronchoconstrictive effects of bradykinin on the human respiratory system,[19] and the enhancement of bradykinin-induced bronchoconstriction in guinea pigs by captopril.[20] Bradykinin augments formation of arachidonic acid derivatives, such as prostaglandins and leukotrienes, which may be involved in ACE inhibitor-induced cough. Despite data that suggest a role of kinin or prostaglandins as a cause of cough, the blood concentrations of PGE_2, $PGF_{2\alpha}$, and TXB_2 during imidapril therapy were not increased in our group 1 patients, who had irritable cough, compared with group 2 and 3 patients. Instead, PGE_2 increased statistically significantly in patients with no cough or mild cough. Administration of sulindac was effective for suppressing imidapril-induced cough in five patients, as reported in previous studies using the nonsteroidal anti-inflammatory drugs sulindac[21] and indomethacin.[22] Thus our results suggest that local, not systemic, activation of the prostaglandin cascade is at least partly responsible for the development of cough associated with ACE inhibitors.

The reason why different ACE inhibitors cause cough at different frequencies of occurrence is still unknown. Imidapril is a long-acting drug lacking a sulfhydryl group. The occurrence of cough is nonspecific for the presence or absence of a sulfhydryl group in the ACE inhibitors. Although the incidence of cough is apparently higher with drugs having a longer duration of action, this association has not been fully established.[10,23] One possibility as to why some ACE inhibitors cause more coughing than others is because of their different potencies for causing inhibition of the hydrolysis of bradykinin and angiotensin I. An in vitro study using ACE purified from canine lung disclosed that the accumulation of bradykinin relative to the inhibition of angiotensin was significantly reduced with imidaprilat as compared with the reduction with enalaprilat, ramiprilat, or captopril.[24] Imidaprilat has also been reported to potentiate the action of bradykinin to a lesser degree than enalaprilat in isolated canine blood vessels.[25] These results suggest that reduced inhibition of bradykinin breakdown may be associated with the milder imidapril-induced coughing noted in this clinical trial.

Rechallenge with administration of enalapril following a washout period was not performed in the present study, and thus the possibility that the cough was not induced by enalapril cannot be eliminated. However, the cessation of irritating cough within 1 week after withdrawal of enalapril

was noticeable, and because clinical examinations excluded other causes of coughing, the cough probably occurred as a result of the enalapril.

In conclusion, this study demonstrated that about 70% of patients who had had active cough with enalapril showed disappearance or improvement of cough for a long period when their medication was replaced with imidapril. Imidapril is a potential alternative ACE inhibitor that can be used in patients who require such drugs but who develop coughs during medication with other ACE inhibitors.

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