Difference in the Incidence of Cough Induced by Angiotensin Converting Enzyme Inhibitors: a Comparative Study Using Imidapril Hydrochloride and Enalapril Maleate

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To compare the incidence of cough between two angiotensin converting enzyme (ACE) inhibitors, imidapril and enalapril, comparative crossover study was performed in 489 patients (228 men and 261 females) with essential or renal parenchymal hypertension. Patients were randomly assigned to one of two treatment groups, a group receiving imidapril for 12 wk (Period I) followed by enalapril for 12 wk (Period II), and a group in which the order of drugs was reversed. The occurrence of cough during treatment was monitored by questionnaire in all cases. There were no differences in background characteristics between the two groups. The incidence of cough during Period I was 15.2% (32/210) in the group initially treated with imidapril (Group IE) and 38.6% (85/220) in the group initially treated with enalapril (Group EI), the difference being statistically significant (p < 0.001). During Period I, decrease in blood pressure was observed in 63.9% (115/180) of Group IE and 64.6% (115/178) of Group EI patients. In approximately half of the patients in Group EI who developed cough during Period I and in whom the treatment was subsequently switched to imidapril, cough subsequently disappeared. It was concluded that the incidence of cough was significantly less under imidapril than under enalapril treatment, while there was no difference in the antihypertensive effects of the two ACE inhibitors.

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Key Words: angiotensin converting enzyme inhibitors, cough, antihypertensive effect

Cough is a common side effect affecting Japanese patients treated with ACE inhibitors, while serious side effects such as angioneurotic edema and anemia are relatively rare. Although the mechanism underlying cough induction is considered to be shared by all ACE inhibitors, its actual incidence varies among individual agents.

Imidapril is a prodrug-type of ACE inhibitor without a sulphydryl (SH-) group developed in Japan (Fig. 1) (1). Clinical observations have suggested that the incidence of cough is low with imidapril (2). According to some studies, cough disappeared or diminished when other ACE inhibitors were replaced with imidapril (3). In the present investigation, we compared the incidence of cough between imidapril and enalapril treatment (enalapril is the most widely prescribed ACE inhibitor in Japan) by means of a crossover study.

Subjects and Methods

Subjects
Ambulatory out-patients with mild to moderate essential or renal parenchymal hypertension who visited any of several clinics or hospitals throughout Japan between April 1995 and March 1996 were recruited. A criterion of inclusion was blood pressure of 160/95 mmHg or higher, and the stability of this...
level during the 4-wk observation period. There were no restrictions on gender or age for inclusion. All participants gave written or verbal informed consent to participate in the study.

Investigation Methods

A randomized two-period crossover study was carried out to compare the occurrence of cough under imidapril and enalapril treatment, as well as to compare the antihypertensive effect of these drugs. Blood pressure was measured two to three times during the 2-4 wk observation period. Patients satisfying the inclusion criteria were administered a questionnaire with items regarding cough. As described below, treatment was initiated after determining the order in which the drugs were to be given by the randomized envelope method. Imidapril hydrochloride was administered as Tanatril® tablets (2.5, 5, and 10 mg) or Novarok® tablets (2.5, 5, and 10 mg), and enalapril maleate was administered as Renivace® tablets (2.5, 5, and 10 mg). Group I received imidapril followed by enalapril, while Group II received the drugs in reverse order. Each of the two drugs was given for 12 wk without a wash-out period between the two treatment periods. In the first treatment period (Period I), oral administration of imidapril or enalapril was started at a dose of 5 to 10 mg once daily. The dose was subsequently adjusted according to the age and the symptoms of individual patients as needed, and the final dose at the end of Period I was used as the starting dose of the second drug at the start of the second treatment period (Period II), followed by readjustment of the dose as in Period I.

When excessive drop or elevation of blood pressure, prolonged lack of antihypertensive effect, worsening of complications, or serious side effects were encountered, the treatment was terminated and the appropriate measures taken. When this occurred during Period I, the treatment was switched to treatment with the other agent whenever possible. Concurrent use of other drugs, including antihypertensive agents other than ACE inhibitors and potassium-sparing diuretics, was allowed as needed, provided that no change in the dose or use of such drugs was made during the study period.

Observation Items

The following parameters were observed according to the protocols in Table 1.

Blood pressure
Blood pressure was measured in the same position during the entire study period. Hypotensive effects were judged by the criteria shown in Table 2.

Onset of cough
During the observation and treatment periods, the patients were queried at 4-wk intervals about the occurrence of cough during the preceding 1 wk using a questionnaire (Table 3).

Evaluation Items and Methods

Comparison of the occurrence of cough
1) Comparison between the groups: The incidence of cough as related to ACE inhibitor administration during Period I was compared between the two treatment groups.
2) Comparison between the treatment periods: The characteristics of the cough episodes (i.e., frequency, duration, and severity) were compared between Period I and Period II, and the results were classified into the following 4 categories: A, Imidapril
Comparison of the antihypertensive effects
1) Comparison between the groups: The average blood pressure at the last two clinic visits of the observation period was compared to the average blood pressure at the last two final clinic visits of Period I. On the basis of the criteria shown in Table 2, the antihypertensive effects of the treatment were classified into the following 4 categories: A, Decreased; B, Slightly decreased; C, No change; D, Increased. When classifications by the systolic and the diastolic blood pressures were inconsistent, the antihypertensive effect was classified by the change in mean blood pressure. When blood pressure decreased to less than 150/90 mmHg, the effect was classified as "decreased" even if the change did not meet the criteria shown in Table 2.

2) Comparison between the treatment periods: The antihypertensive effects of the drug were compared between Period I and Period II, and the results were classified into the following 4 categories: A, Imidapril showed better hypertensive effects; B, The effects of imidapril and enalapril were similar; C, Enalapril showed better effects; D, Classification not possible.

Statistical Methods
Patient backgrounds were compared using Fisher’s exact test, chi square test, and Wilcoxon’s rank sum test. The incidence of cough was compared by Fisher’s exact test and the antihypertensive effects by Wilcoxon’s rank sum test. A two-tailed test was also used. Significance was determined at the $p < 0.05$ level.

Results

Patient Backgrounds
A total of 539 patients were originally recruited to the study. Fifty of these were excluded for various reasons (including violation of the envelope method in 32 cases). Of the remaining 489 patients, 246 were assigned to receive imidapril followed by enalapril (Group IE), and 243 to receive enalapril followed by imidapril (Group EI). There were no significant differences in background characteristics between Groups IE and EI (Table 4).

Evaluation
Comparison between the two groups during Period I
1) Incidence of cough
The incidence of cough during Period I was evaluated in 210 of the 246 patients in Group IE and in 220 of the 243 patients in Group EI (Table 5). Cough occurred in 15.2% (32/210) of Group IE and in 38.6% (85/220) of Group EI patients (Table 4), and the difference was highly significant ($p < 0.001$).

2) Antihypertensive effects
There was no significant difference in the antihypertensive effects of the treatment between the two groups (Table 6). The blood pressure response to the treatment was classified as "decreased" in 63.9% (115/180) and 64.8% (115/178) of Group I and Group II patients, respectively.

Comparison between the treatment periods
1) Comparison of the incidence of cough
Comparison of the states of cough between Period I and Period II was possible in 349 patients, but in 212 of these patients, no coughing was observed throughout Periods I and II. In 97 of the 349 patients (27.8%), imidapril was considered more effective than enalapril, while enalapril was considered superior in 6 of the 349 (1.7%). In 34 patients (9.7%), imidapril and enalapril were considered similar in terms of inducing cough.

2) Comparison of the antihypertensive effects
The antihypertensive effects could be compared between Period I and Period II in 287 patients. In 21.6% (62/287) of these patients, imidapril was considered more effective than enalapril, while in 17.1% (49/287) enalapril was considered more effective than imidapril. In 59.6% (171/287), the antihypertensive effects of the two drugs were considered similar.
Data Concerning the State of Cough

Changes in the incidence of cough

1) Group IE

Cough developed in 32 of the 210 patients in Group IE who were adequately evaluated for cough during Period I (Table 5). In 11 of these 32, a decision was made not to switch to enalapril treatment, and thus these 11 patients did not proceed to Period II of the study. In the remaining 21 patients, although imidapril was switched to enalapril, cough persisted in all cases.

Group EL

In Group EL, cough developed in 85 of the 220 patients adequately evaluated for cough during Period I (Table 5). In 15 of these 85, the treatment was not switched to imidapril. In the remaining 70, enalapril was switched to imidapril, with the result that cough disappeared in 37 patients (52.9%).

The characteristics of cough during Period I

Questionnaire responses regarding the state of cough during Period I are summarized in Tables 7 through 9.

1) Number of cough episodes per d (Table 7)

Cough lasting throughout the day was reported in only 1.0% (21206) of the patients on imidapril (Group IE) and in as much as 5.6% (121214) of the
patients on enalapril (Group El).
2) Number of days with cough per wk (Table 8)
Cough occurred almost everyday in 9.7% (20/207) of the patients on imidapril (Group IE) and in 22.4% (48/214) of those on enalapril (Group El).
3) Severity of cough (Table 9)
Severe cough was present in 1.0% (2/208) of the patients on imidapril (Group IE), and in 5.1% (11/214) of the patients on enalapril (Group El).

Discussion
ACE inhibitors are widely used throughout the world to treat not only essential hypertension but also hypertension associated with heart failure or renal disorders, since the inhibition of angiotensin II production and elevation of bradykinin and prostaglandins by these agents provide both potent antihypertensive effects and renal and cardiac protection. It has recently been shown that ACE inhibitors are more effective than other antihypertensive drugs in preventing the relapse of myocardial infarction, in improving the prognosis of heart failure, and in preventing the progression of diabetic nephropathy, leading to their wider use in various cardiovascular disorders. Along with this increased use, however, it is evident that the occurrence of cough associated with ACE inhibitors is more common than previously thought, although the incidence and severity of cough vary among the different ACE inhibitors. The pathogenesis of cough due to ACE inhibitors remains speculative, but it has been proposed that increased endogenous bradykinin and substance P in the airway mucosa stimulate airway receptors and enhance cough reflex in subjects with airway hypersensitivity (4).

In clinical practice, it is difficult to accurately document the incidence of cough in patients being treated with ACE inhibitors. Such incidence has been variously reported as between 2% and 30% of patients (2, 3, 5-8), possibly reflecting differences in the agents used, the subject groups treated, and the survey methods.

In a pre-market trial of imidapril, the overall incidence of cough was reported as 2.8% (2). This figure is generally considered remarkably low, given that, at the time of the trial, this side effect had already been well documented for other ACE inhibitors already on the market, and thus was given especial attention in the trial. The pre-market trial consisted of a double-blind study in which antihypertensive and side effects of imidapril were compared to those of enalapril, with the result that the incidence of cough was 0.9% with imidapril and 7.0% with enalapril, the difference being highly significant (2). These findings suggested that the incidence of cough should be lower with imidapril than with any other ACE inhibitors, for which the reported incidences of cough range between 5.6% and 12.6%.

Sasakuri et al. reported that, in 47.9% of patients in whom cough developed while on other ACE inhibitors, cough disappeared after switching to imidapril (3). In the present study, we conducted a nationwide multi-center survey on the incidence of cough due to imidapril using enalapril as a control drug. Considering the results of the previous study by Sasakuri et al. (3), the following measures were taken in the present study:
1) A detailed questionnaire on the occurrence of cough was administered to each patient.
2) Prior to the study, all patients were informed about the possible occurrence of cough.
3) Patients were randomly assigned to one of two
The incidence of imidapril-induced cough was 15.2% for imidapril and 38.6% for enalapril, the percentage being approximately 2.5 times higher for the former drug, and the difference being of high statistical significance. In the group treated initially with imidapril (Group IE), 32 patients developed cough during Period I. Imidapril was switched to enalapril in 21 of these cases, but cough persisted in all. Meanwhile, in the group treated initially with enalapril (Group EI), cough developed during Period I in 85 patients. Disappearance of cough was observed in approximately half of the 70 of these 85 patients who were subsequently switched to imidapril. In addition, analysis of the questionnaire items concerning cough incidence over Period I indicated that the severity, frequency, and duration of cough were all greater with enalapril than with imidapril.

The incidence of imidapril-induced cough was 15.2% during Period I, a percentage much higher than that previously reported (2). This difference can be attributed to the fact that all of our patients were informed during the consent process about the possible occurrence of cough during treatment, and also to the fact that frequent inquiries were made about cough via the questionnaire. Nevertheless, the incidence of cough with imidapril was less than that with enalapril in the present study. Furthermore, cough disappeared in more than half of patients by switching from enalapril to imidapril. In addition, imidapril improved both the frequency (the number of episodes per d as well as the number of episodes per wk) and the severity of cough in approximately 65% of patients, as revealed by the questionnaire results.

These results strongly indicate that use of imidapril is associated with much lower incidence of cough than use of standard ACE inhibitors, and that cough severity is also reduced by imidapril.

Town et al. reported that cough occurred in 25% of patients receiving captopril and in 33% receiving enalapril (9), while Woo et al. reported cough incidences of 46% and 42% for these two agents, respectively (10). In Japan, Hirota and Tatsuoka reported that the incidence of cough was 17.8% for enalapril (11). The incidence of cough reported in these studies is comparable to that reported here, but might have been much higher if some of the present measures had been utilized for greater accuracy.

Imidapril and enalapril decreased blood pressure in 63.9% and 64.6% of patients, respectively during Period I in the present study, indicating that the antihypertensive effects of the two agents are comparable. Comparison between Periods I and II also indicated that the antihypertensive effects of the two drugs were similar.

In conclusion, the present study indicates that imidapril is less likely to induce cough than enalapril, while the antihypertensive effects of the two drugs are comparable. It is suggested that imidapril will enhance the quality of life of patients to be treated with ACE inhibitors.

References