Comparison of the Incidence of Imidapril and Enalapril Induced Cough

Warangkna Boonyapisit MD*,
Damras Tresukosol MD*

**Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Background: *Imidapril is an angiotensin converting enzyme (ACE) inhibitor without a sulfhydril group which has been shown from previous study to have low incidence of ACE inhibitor induced cough.*
Objective: *To compare the incidence of cough between two ACE inhibitors, imidapril and enalapril*
Material and Method: *A comparative cross over study was performed in 119 patients with hypertension or left ventricular dysfunction. Patients were assigned to one of the two treatment groups, either a group receiving imidapril or enalapril for 4 weeks (Period I) and then these same groups were crossed over to receive either enalapril or imidapril for 4 weeks (Period II). The occurrence of cough during treatment was monitored by interviewing the patients.*
Results: *The incidence of cough was 44 % while on imidapril treatment and 66% while on enalapril treatment (p = 0.0014). The antihypertensive effects of two drugs were not different.*
Conclusion: *The incidence of cough was significantly less under imidapril than under enalapril treatment, while there was no difference in the antihypertensive effects between the two ACE inhibitors.*

Keywords: *Angiotensin converting enzyme inhibitors, Angiotensin converting enzyme inhibitors induced cough*

J Med Assoc Thai 2010; 93 (Suppl. 1): S48-53
Full text. e-Journal: *http://www.mat.or.th/journal*

Angiotensin converting enzyme (ACE) inhibitors are first line drugs used for the treatment of hypertension and left ventricular (LV) dysfunction. As their efficacy is well proven, their additional advantage is particularly well tolerated. However, cough is a disturbing adverse effect of ACE inhibitors. Incidence of cough induced by ACE inhibitors has been reported over a wide range (3-44%)[1,2]. Chinese in Hong Kong have high prevalence of persistent cough reported in 44% of patients taking ACE inhibitors (46% of those receiving captopril and 41.8% of patients taking enalapril)[2]. In Thailand, Buranakitjaroen P et al reported incidence of cough induced by ACE inhibitors range from 23.6 to 31.3%[3].

Imidapril is a new ACE inhibitor without a sulfhydril group. Clinical observations have suggested that the incidence of cough is low with imidapril. Previous studies in Japan report that the incidence of cough was significant less under imidapril than under enalapril treatment[4-6]. The purpose of the study is to compare the incidence of cough between imidapril and enalapril treatment.

Correspondence to: Boonyapisit W, Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. E-mail: waran_byps@yahoo.com

Material and Method

Patients

Between July 2001 and October 2001, 119 patients who had hypertension or LV dysfunction were enrolled. Inclusion criteria were LV dysfunction with left ventricular ejection fraction (LVEF) < 40%, new cases of hypertension (BP ≥ 140/90 mmHg) or patients with history of hypertension, who were at that time under treatment with antihypertensive medications. Exclusion criteria were history of chronic cough of any reason, pregnancy and renal dysfunction (serum creatinine> 3 mg/dl).

Study Design

The study design was an open labeled 4 weeks comparative cross over study.

Material and Method

All the patients enrolled who met the inclusion criteria were randomized by simple randomization into 2 sequences, sequence I (IE) received imidapril (I) followed by enalapril (E), while sequence II (EI) received the same drugs in reverse order. Each of 2 drugs was given for 4 weeks without a wash out period between the 2 treatment periods.

Written informed consent was obtained. At baseline, the patients were interviewed to obtain their baseline characteristics. The information collected was age, coronary artery disease (CAD) risk factor, current antihypertensive drugs, history of ACE inhibitor use and history of cough when using ACE inhibitor.

In period I, drug was started at dose 5-10 mg/day for imidapril and 10-20 mg/day for enalapril. Imidapril hydrochloride was administered as Tanatrila tablet (5 and 10 mg) and enalapril maleate was administered as Reniteca tablet (10 and 20 mg). The dosage was adjusted during follow-up according to BP as needed. Concurrent use of other drugs, including other antihypertensive agents was allowed as needed, but no change in the dose was allowed during study period. None of the patients received 2 drugs in ACE inhibitor group at the same time. When serious side effects occurred or a patient could not tolerate the cough, the treatment was terminated for that patient.

Blood pressure was measured in sitting position at baseline, the end of period I (Day 30) and the end of period II (Day 60).

Cough severity is evaluated by using rating scale into mild (1-3 times/day), moderate (4-10 times/day) and severe (>10 times/day or self withdrawal of medication) at baseline, end of period I and II. The cough was presumed to be ACE inhibitor related when it persisted more than 2 weeks after the medication was initiated without other signs and symptoms of respiratory tract infection.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences-version 10.0 (SPSS10.0). Patient baseline characteristics were compared between the 2 sequences using student t test and Chi-square test. The incidence of cough and blood pressure control were compared by Chi-square test. Difference were considered statistically significant if $p < 0.05$.

Results

One-hundred and nineteen patients were enrolled. Sixty-nine patients were in sequence I that received initial treatment with imidapril followed by enalapril. Fifty patients were in sequence II that received initial treatment with enalapril followed by imidapril.

The baseline characteristics of the 119 patients included in the analyses are given in Table 1.

No differences were observed between the two groups in age, sex, CAD risk, previous treatment of antihypertensive drugs and severity of hyperten-

Table1. Baseline Characteristics of study groups

	Initial treatment with Imidapril	Initial treatment with Enalapril	p-value
n	69	50	
Age, year	65.37 ± 10.05	65.2 ± 7.89	0.92
Sex (male/female)	34/35	27/23	0.747
DM	25	15	0.607
HT	63	47	0.732
Dyslipidemia	32	30	0.20
Smoking	2	5	0.129
Family history of CAD	7	7	0.722
Diagnosis			0.732
-HT	63	47	
-LV dysfunction	6	3	
Previous use of ACE inhibitor	20	15	0.93
Cough when use ACE inhibitor	12	6	0.581
Previous antihypertensive drugs			
-Beta blocker	40	35	0.25
-Calcium channel blocker	34	20	0.414
-Hydrochlorothiazide	14	9	0.939
-Alpha blocker	1	2	0.572
-Angiotensin II receptor blocker	9	2	0.117
-Other drugs	2	2	1.00
Systolic BP	160.07 ± 21.43	155.96 ± 21.39	0.303
Mean BP	111.3 ± 10.58	109.93 ± 14.77	0.674
Diastolic BP	88.91 ± 12.37	89.56 ± 12.67	0.781
Severity of HT (WHO-ISH) 6			
-Grade I (mild)	15	15	0.472
-Grade II (moderate)	32	18	
-Grade III (severe)	15	9	

sion.

Eleven patients dropped out of the study in the end of period I. Nine patients in imidapril group (2 patients due to personal reason, 7 patients due to cough) vs. 2 patients in enalapril group due to cough.

The antihypertensive effects of two drugs are shown in Table 2, 3 and Fig. 1. There was no significant difference in the antihypertensive effects of the treatment between the two groups.

Cough occurred in 51 of the 116 patients (44%) while on imidapril treatment (include the data from both period I and II) and 72 of the 109 patients (66%) while on enalapril treatment (include the data from period I and II), and the difference was statistically significant ($p = 0.0014$) (Table 4).

Table 5 showed severity of cough. Severe cough (> 10 times/day) occurred in 20 of the 116 patients (17%) while on imidapril treatment and 36 of the 109 patients (33%) while on enalapril treatment ($p = 0.009$).

Other adverse events were dizziness in one patient in imidapril group and one patient in enalapril group, as well as palpitation and flushing in one patient in the enalapril group. No serious adverse events occurred during the study.

In this study there were 18 patients who previously used ACE inhibitors and had developed cough from previous ACE inhibitors. 12 patients were in the group that received initial treatment with imidapril (group I) and 6 patients were the group that received initial treatment with enalapril (group II). In this subgroup, we found the incidence of cough was 44.44% (8 of 18 patients) while on imidapril treatment and 93.75% (15 of 16 patients) while on enalapril treatment ($p = 0.006$). 2 patients in the group that initial treatment with imidapril group were eliminated because of intolerable cough.

Discussion

The mechanisms of ACE inhibitors induced cough remain unclear. Bradykinin, substance P, prostaglandins or thromboxane[7-9] have been suggested to be involved. Both bradykinin and substance P are degraded by angiotensin converting enzyme to inactive metabolites. Inhibition of ACE will increase their levels. Bradykinin may induce bronchial irritation and cough via enhanced production of prostaglandins, which may then stimulate afferent C-fibers in the air-

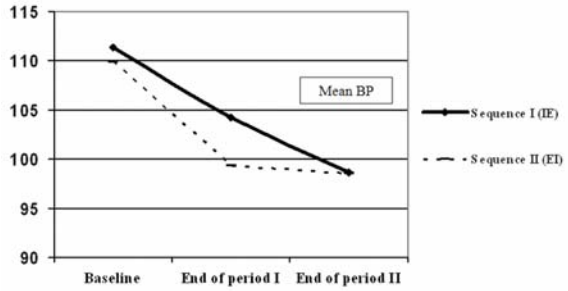

Fig 1. Blood pressure control

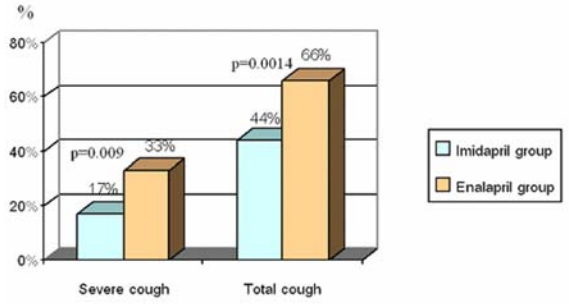

Fig 2. Compare incidence of cough and severe cough between imidapril and enalapril treatment

Table 2. Blood pressure control

Blood pressure (mmHg)	Baseline BP(mmHg)	End of period I BP(mmHg)	End of period II BP(mmHg)
Systolic BP			
-Imidapril	160.07 ± 21.43	151.43 ± 30.21	144.79 ± 20.8
-Enalapril	155.96 ± 21.39	145.51 ± 20.65	146.11 ± 23.75
Diastolic BP			
-Imidapril	88.91 ± 12.37	81.47 ± 13.19	80.90 ± 14.35
-Enalapril	89.56 ± 12.67	80.69 ± 12.90	80.62 ± 15.43
Mean BP			
-Imidapril	111.3 ± 10.58	104.26 ± 16.57	98.51 ± 12.92
-Enalapril	109.93 ± 14.7	99.34 ± 14.39	98.66 ± 16.98

way[9-11]. Previous study found that ACE inhibitors had different potencies for inhibiting hydrolysis of bradykinin, and there was less accumulation of bradykinin with imidapril than with captopril, enalaprilat and ramiprilat[6].

The reported incidence of cough due to treatment with ACE inhibitors has varied greatly depending on the method of collection[12-15]. For example cough attributed to enalapril has been reported as low as 2.8%[16] and 2.9%[17] in post marketing surveillance and in 7-25% of subjects from hospital (university based referral center and private practice) surveys[14]. The incidence of cough in our study, which is 66% in enalapril group and 44% in imidapril group, is much higher than previous reports. The high incidence of cough in our study may be due to the fact that our study design is a prospective study that asked patients to respond to specific question about cough. The previous data of ACE inhibitors induced cough in Thailand showed prevalence of cough is higher in prospective study[3]. Second, the incidence of cough is higher in Chinese, based on a study from Hong Kong[2], which showed incidence of cough 41.8% in patients taking enalapril. Asian patients may be more susceptible to ACE inhibitor induced cough than other racial group. Racial differences in pharmacokinetics and pharmacodynamics for ACE inhibitors may exist. Third, in our study the severity of cough was grading into mild (1-3 times/day), moderate (4-10 times/day) and severe (>10 times/day) and the incidence of severe cough was 33% in enalapril group and 17% in imidapril group which were not much higher from the incidences of cough reported in prior reports. It is possible that cough < 10 times/day might not be noticed by the patients if we did not asked specific questions about cough.

Table 3. Change of blood pressure

Blood pressure (mmHg)	Baseline BP (mmHg)	Change of BP (mmHg)	p-value
Systolic BP			
-Imidapril	160.07 ± 21.43	-12.0	0.793
-Enalapril	155.96 ± 21.39	-10.89	
Diastolic BP			
-Imidapril	88.91 ± 12.37	-8.15	0.889
-Enalapril	89.56 ± 12.67	-8.48	
Mean BP			
-Imidapril	111.3 ± 10.58	-9.44	0.953
-Enalapril	109.93 ± 14.7	-9.28	

Table 4. Incidence of cough

	Cough	Without cough	Total	Incidence	p-value
Imidapril group	51	65	116	44%	0.0014
Enalapril group	72	37	109	66%	

Table 5. Severity of Cough

Severity	Mild (1-3 times /day)	Moderate (4-10 times /day)	Severe (>10 times /day)	Total cough	Without cough
Imidapril group	23	8	20	51	65
Enalapril group	13	23	36	72	37

Our study showed that incidence of cough when on imidapril treatment was significantly lower than when on enalapril treatment. In the subgroup of patients who previously received ACE inhibitors and had cough, we found that almost all patients (15 from16 patients) had cough while receiving enalapril but only about half of patients (8 from 18 patients) had cough while receiving imidapril. Although the number of patients in this subgroup is small, this result suggests that imidapril may be one of the alternative drugs for patients who develop intolerable cough on other ACE inhibitors. Further study focused on this specific group of patients is needed to prove the hypothesis.

The antihypertensive effect of imidapril and enalapril in this study were not difference and there was no serious side effect which occurred in the study in either group.

In conclusion, the present study shows that imidapril is less likely to induce cough than enalapril, while the antihypertensive effects of the two drugs are not different. The incidence of cough in this study was higher than in previous reports, which may be secondary to the fact that the study was a prospective study, asking specific question about cough. A well randomized double-blind control trial with an open question about the adverse effect of the drugs should be conducted to confirm this result in further study.

References

1. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin converting

enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med 1992; 117:234.
2. Woo KS, Nicholls MG. High prevalence of persistent cough with angiotensin converting enzyme inhibitors in Chinese. Br J Clin Pharmacol 1995; 40:141.
3. Buranakitjaroen P, Sriussadaporn S, Phoojaroenchanachai M, et al. Angiotensin converting enzyme inhibitor induced cough: experience in Siriraj Hospital. J Med Assoc Thai. 2003; 86: 647-54.
4. Saruta T, Arakawa K, Iimura O, et al. Difference in the incidence of cough induced by angiotensin converting enzyme inhibitors: a comparative study using imidapril hydrochloride and enalapril maleate. Hypertensions Res 1999; 22: 197-202.
5. Saruta T, Omae T, Kuramochi M, et al. Imidapril hydrochloride in essential hypertension: a double-blind comparative study using enalapril maleate as a control. J hypertens 1993; 13 (Suppl 3): S23-30.
6. Sasaguri M, Idei shi M, Kinoshita A, et al. Differential inhibition of bradykinin hydrolysis by four ACE inhibitors: a possible explanation for differences in induced coughing. Hypertens Res 1994; 17: 253-58.
7. Tomaki M, Ichinose M, Miura M, et al. Angiotensin converting enzyme inhibitor-induced cough and substance P. Thorax 1996; 51: 199-201.
8. Malini PL, Strocchi E, Zanardi M, et al. Thromboxane antagonism and cough induced by angiotensin-converting-enzyme inhibitor. Lancet 1997; 350: 15.
9. Ichinose M, Nakajima N, Takahashi T, et al. Protection against bradykinin- induced bronchoconstriction in asthmatic patients by neurokinin receptor antagonist. Lancet 1992; 340: 1248-1.
10. Wood RC. Bronchospasm and cough as adverse reactions to the ACE inhibitors captopril, enalapril and lisinopril. A controlled retrospective cohort study. Br J clin Pharmac 1995; 39: 265-70.
11. Lunde H, Hedner T, Samuelsson O, et al. Dyspnea, asthma, and bronchospasm in relation to treatment with angiotensin converting enzyme inhibitors. Br Med J 1994; 308: 18-21.
12. Yeo WW, Ramsay LE. Persistent dry cough with enalapril: incidence depends in the method used. J Human Hypertens 1990; 4: 517-20.
13. Yeo WW, Maclean D, Richardson PJ, Ramsay LE. Cough and enalapril: assessment by spontaneous reporting and visual analogue scale under double-blind conditions. Br J clin Pharmac 1991; 31: 356-9.
14. Simon SV, Black HR, Moser MV, et al. Cough and ACE inhibitors. Arch Intern Med 1992; 152: 1698-700.
15. Sebastian JL, McKinney WP, Kaufman J, Young MJ. Angiotensin-converting enzyme inhibitors and cough. Chest 1991; 99:36-9.
16. Coulter, DM, Edwards IR. Cough associated with captopril and enalapril. Br Med J 1987; 294: 1521-2.
17. Inmann WHW, Rawson NSB, Wilton LV, et al. Postmarketing surveillance of enalapril. I: Results of prescription event monitoring. Br Med J 1988; 297: 826-9.

การเปรียบเทียบอุบัติการณ์การไอที่เกิดจากยา Imidapril และ ยา Enalapril

วรางคณา บุญญพิสิฏฐ์, ดำรัส ตรีสุโกศล

วัตถุประสงค์: *เพื่อเปรียบเทียบอุบัติการณ์การเกิดการไอที่เกิดจากยา Angiotensin converting enzyme (ACE) inhibitor 2 ชนิดคือ ยา Imidapril ซึ่งไม่มีอนุพันธ์ Sulfhydril และ ยา Enalapril*

วัสดุและวิธีการ: *คณะวิจัยได้ศึกษาผู้ป่วย 119 รายที่มีโรคความดันโลหิตสูง หรือมีการบีบตัวของหัวใจห้องล่างซ้ายลดลง ผู้ป่วยจะได้รับการแบ่งเป็น 2 กลุ่ม โดยกลุ่มที่ 1 ได้รับยา Imidapril และ กลุ่มที่ 2ได้รับยาEnalapril ในช่วง 4 สัปดาห์แรกของการศึกษา (การศึกษาช่วงที่ 1) ต่อมาจะมีการสลับกลุ่มโดยกลุ่มที่1 จะเปลี่ยนเป็นได้ยา Enalapril และกลุ่มที่2 เปลี่ยนเป็นได้ยา Imidapril (การศึกษาช่วงที่ 2) โดยอาการไอที่เกิดขึ้นระหว่างได้รับยาในแต่ละช่วงจะได้รับการเก็บข้อมูลจากการสัมภาษณ์ผู้ป่วย*

ผลการศึกษา: *พบอุบัติการณ์การไอ 44% ในผู้ป่วยที่ได้รับยา Imidapril และ 66%ในผู้ป่วยที่ได้รับยา Enalapril ($p = 0.0014$) ฤทธิ์ลดความดันของยา 2 ตัวไม่แตกต่างกัน*

สรุป: *อุบัติการณ์การเกิดการไอระหว่างได้ยา Imidapril น้อยกว่า Enalapril อย่างมีนัยสำคัญทางสถิติ ในขณะที่ฤทธิ์ลดความดันไม่ต่างกัน*