Angiotensin Converting Enzyme Inhibitor Induced Cough : Experience in Siriraj Hospital

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Abstract

With the increasing use of angiotensin converting enzyme inhibitors (ACEI) in the treatment of hypertension, particularly in diabetic patients, and heart failure, an annoying cough has frequently been observed. According to the post marketing surveillance studies, the prevalence of cough associated with ACEI was only 0.1-4 per cent. However, many recent studies have observed a very much higher frequency. To examine the incidence and pattern of cough associated with the usage of ACEI (C-ACEI) in a Thai population, mixed retrospective and prospective studies were performed in hypertensive patients who attended the out-patient department, Siriraj Hospital between December 1999 and August 2000. A thousand cases who had used or have been using ACEI were studied. C-ACEI was present in 179 cases of 760 retrospective studied cases (23.6%) and 75 cases of 240 prospective studied cases (31.3%). Cough was typically described as irritative (93.8% retrospectively and 98.7% prospectively, $p = 0.05$) and nocturnal in onset (74.9% retrospectively and 80% prospectively, $p = 0.12$), and usually appeared within the first 4 weeks of treatment (41.3% retrospectively and 46.7% prospectively, $p = 0.43$). Patients who received a full dosage of ACEI did not have to posses an increasing risk of C-ACEI. There was no difference in the prevalence of C-ACEI among types of ACEI, except cilazapril and quinapril which were found to be higher than enalapril in the retrospective study ($p < 0.0001$ and $p = 0.002$, respectively). Types of study were shown to influence the prevalence of C-ACEI. Prospective studies yielded a higher rate of C-ACEI than retrospective ones.

Key word : Cough, ACE Inhibitor

BURANAKITJAROEN P, SRIUSSADAPORN S,
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J Med Assoc Thai 2003; 86: 647-654

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Angiotensin converting enzyme inhibitors (ACEI) had been shown to be highly effective in the treatment of congestive heart failure (CHF) by reducing pre-load and after-load pressure[1,2], nephropathy by reducing intraglomerular pressure and reducing proteinuria[3,4], and diabetes mellitus (DM) by improving insulin sensitivity[5]. More importantly, ACEI's had been shown to reduce clinical outcomes associated with hypertension such as stroke[6,7], cardiovascular events[7], and new onset of DM[7,8]. Unfortunately, a large number of patients experience adverse drug effects that limit the long-term usage of ACEI's. The most troublesome is a persistent dry cough, the prevalences of which were reported differently among trials[7,9-12]. Cough has been reported with low prevalence in many post marketing surveillance studies, ranging from only 0.1 per cent (early studies) to 4.0 per cent[13-16], while the prevalence of cough reported in recent published literature were remarkably higher[7,12]. Surprisingly, it was not even commented on in the study by Croog et al on the effects of antihypertensive therapy on the quality of life[17]. The present study was carried out to obtain the epidemiological data on the incidence and pattern of cough associated with the usage of ACEI (C-ACEI) among Thai hypertensive patients.

PATIENTS AND METHOD

This study was carried out both retrospectively and prospectively. The prevalence of C-ACEI was examined in a 1000-aimed case study. Medical records of hypertensive patients who attended the General Medicine Clinic and Hypertension Clinic, Siriraj Hospital were reviewed whether ACEI was prescribed as a part of treatment regimens. If the screening patients had taken ACEI regularly, the possibility of C-ACEI would be looked for (retrospective cases). Meanwhile, an open-labeled study was also conducted simultaneously (prospective cases) in cases whose ACEI was not previously given and their clinical characteristics were considered to get benefit from ACEI such as diabetes, proteinuria etc. Treatment with ACEI was then initiated. Clinical responses and adverse effects were monitored for at least 6 months. It was not considered as a case of C-ACEI, if no cough developed within the study period. Types of ACEI were chosen arbitrarily by physicians. Patients suffering from respiratory tract diseases such as chronic obstructive pulmonary disease or bronchial asthma were excluded from the study. Patients with a previous history of hyperkalemia, renal insufficiency or allergy to ACEI were also excluded.

Surveillance of C-ACEI was systematically performed from 25th December 1999 until a total of 1,000 cases were achieved. C-ACEI was defined according to the following criteria: cough occurred during the usage of ACEI, no obvious symptoms and signs of upper respiratory tract infection such as fever, nasal stuffiness, runny nose, or sore throat and cough had to be resolved completely within 2 weeks after discontinuation of ACEI. Re-challenge of ACEI could not be performed as previously planned because of the patients' unwillingness. Characteristics of C-ACEI e.g. onset, type of cough (dry or productive), paroxysmal or nocturnal, and accentuation of cough were examined. In addition, cough rates resulting from different ACEI usage were also studied.

Statistical analyses

Results were demonstrated as mean $\pm$ SD or per cent (%) where appropriate. Statistical analyses were performed using Statistical Packages for Social Sciences (SPSS) version 9.0. Student's *t*-test and Chi-square test were used to compare the continuous and categorical data respectively. Univariate analyses were performed to identify the risks in developing C-ACEI. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 1,000 hypertensive patients who had received or were receiving ACEI treatment were recruited by the end of August 2000. Seven hundred and sixty cases (76%) and 240 cases (24%) were enrolled retrospectively and prospectively. The mean age of those retrospective studied patients was 58.2 $\pm$ 11.3 years (19-86 years), of whom 476 cases (62.6%) were females, while that of the prospective studied patients was 59.9 $\pm$ 11.2 years (26-94 years), of whom 149 cases (62.1%) were females. One hundred and seventy nine retrospective studied patients (48 males and 131 females) had records of C-ACEI (23.6%), whereas 75 patients (23 males and 52 females) studied prospectively were diagnosed to have C-ACEI (31.3%) (31.3% *vs* 23.6%, p = 0.02, OR = 1.5, 95% CI = 1.1-2.1). There were no significant differences in the mean age between C-ACEI and non C-ACEI groups among both retrospective (58.4 $\pm$ 10.7 years *vs* 58.1 $\pm$ 11.4

years, p = 0.29) and prospective type of studies (60.7 ± 11.0 years *vs* 59.5 ± 11.3 years, p = 0.97). After taking ACEI, there was a significant increase in the prevalence of C-ACEI among females compared to males in the retrospective study (27.5% *vs* 16.9%, p = 0.001, OR = 1.9, 95% CI = 1.3-2.8). On the contrary, there was no significant difference in the prevalence of C-ACEI between females and males in the prospective study (34.9% *vs* 25.3%, p = 0.12, OR = 1.6, 95% CI = 0.9-3.0) (Table 1).

Cough might occur at any time from the 1st week to the 32nd week in the retrospective study and from the 1st week to the 24th week in the prospective counterpart. It commonly occurred within the first 4 weeks of treatment in both retrospective and prospective studies (41.3% *vs* 46.7%, p = 0.43) (Fig. 1). There were only 3 retrospective cases (1.7%) who developed C-ACEI after 24 weeks, 1 case in the 28th week and 2 cases in the 32nd week. In the retrospective study, 134 cases reported that cough occurred during the nocturnal period (74.9%), while 43 cases reported it occurred all the time (24.0%) (74.9% *vs* 24.0%, p < 0.0001, OR = 9.7, 95% CI = 5.8-16.3). Only 2 cases reported that the cough occurred during the daytime (1.1%). Similarly, 60 cases had cough during the nocturnal period (80%) and 15 cases had a cough all the time (20%) from the prospective study (80.0% *vs* 20.0%, p < 0.0001, OR = 16.0, 95% CI = 6.7-38.9). There was no significant difference in the nocturnal onset of cough between retrospective and prospective data (p = 0.12). The cough was mostly described as irritative in character (93.8% retrospectively and 98.7% prospectively, p = 0.05). The prevalence of cough associated with types of ACEI usage is shown (Table 2).

A significant higher prevalence of female gender was observed in the retrospective study when the C-ACEI was compared to the non C-ACEI groups

Table 1. Prevalence of cough associated with ACEI by gender.

	All/total (n)	%	Male/total (n)	%	Female/total (n)	%	P-value**
Retrospective study	179/760	23.6	48/284	16.9	131/476	27.5	0.001*
Prospective study	75/240	31.3	23/91	25.3	52/149	34.9	0.12
p-value***	0.02*		0.11		0.10		

* p-value considered significant at 0.05
** p-value compared between male and female
*** p-value compared between prospective and retrospective data
n = number of cases

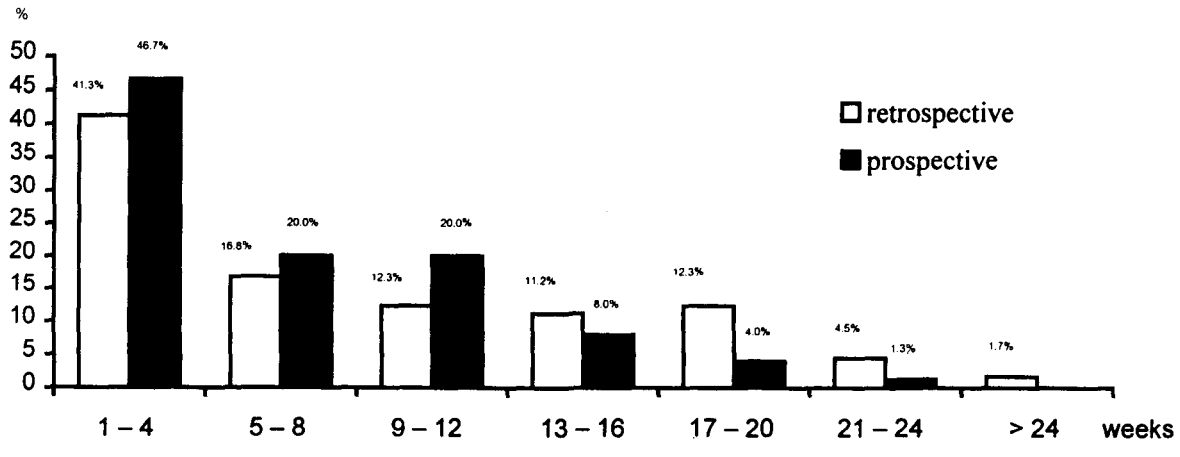

Fig. 1. Onset of cough associated with ACEI, all cases.

Table 2. Prevalence of cough associated with types of ACEI usage during retrospective and prospective studies.

	Retrospective study (760 cases)				Prospective study (240 cases)		
	Cases (n)	C-ACEI (%)	Non C-ACEI (%)	P-value**	Cases (n)	C-ACEI (%)	Non C-ACEI (%)
Enalapril	524	20.3	79.7		215	30.7	69.3
Captopril	35	20.0	80.0	0.97	14	21.4	78.6
Cilazapril	36	52.8	47.2	< 0.0001*	2	0	100.0
Quinapril	79	35.4	64.6	0.002*	3	60.7	39.3
Ramipril	32	15.6	84.4	0.53	6	66.7	33.3
Fosinopril	17	41.2	58.8	0.60			
Lisinopril	21	19.1	80.9	0.58			
Perindopril	16	18.8	81.2	0.89			

* p-value considered significant at 0.05
** p-value compared with enalapril

Table 3. Univariate analyses of patients' characteristics and prevalence of cough.

	C-ACEI	Non-C-ACEI	P-value**	OR	95% CI
Retrospective study (n = 760)	n = 179	n = 581			
Female (%)	73.2	59.4	0.001*	1.9	1.3-2.8
Elderly (%)	64.8	61.5	0.42	1.2	0.8-1.6
Prospective study (n = 240)	n = 75	n = 165			
Female (%)	69.3	58.8	0.12	1.6	0.9-3.0
Elderly (%)	72.0	67.9	0.52	1.2	0.7-2.2

* p-value considered significant at 0.05
** p-value compared between C-ACEI and non-C-ACEI
n = number of cases

(73.2% *vs* 59.4% p = 0.001, OR = 1.9, 95% CI = 1.3-2.8), whereas there was only a trend in the prospective study (69.3% *vs* 58.8%, p = 0.12, OR = 1.6, 95% CI = 0.9-3.0) (Table 3). There was no preponderance of C-ACEI in the elderly (age > 55 years) (Table 3). The onset of C-ACEI was then analyzed according to the dosage of ACEI. The dosages of ACEI's considered to be low were captopril of ≤ 50 mg/d, enalapril of ≤ 5 mg/d, cilazapril of ≤ 2.5 mg/d, fosinopril of ≤ 10 mg/d, lisinopril of ≤ 5 mg/d, perindopril of ≤ 2 mg/d, quinapril of ≤ 5 mg/d, and ramipril of ≤ 2.5 mg/d. C-ACEI was found in 58.1 per cent (104/179) of patients who used low dosages when studied retrospectively and 56.0 per cent (42/75) in the prospective study. It appeared that the rates of cough were very high in the first 4 weeks in both the low and high dosage groups. In the prospective study, the rate of C-ACEI in the low dosage group was higher than the high dosage group (50.0% *vs* 42.4%, p = 0.15). On the contrary, it was the opposite when comparing the rate of C-ACEI among the low to the high dosage groups (38.5% *vs* 45.3%, p = 0.41). The rates of C-ACEI were gradually found less thereafter in both groups (Table 4).

DISCUSSION

Cough is a frequent adverse event of ACEI which creates a lot of trouble, embarrassment and anxiety to the patients. This usually leads to unnecessary investigations and treatments. Among white patients who received ACEI, the prevalence of cough was 5 per cent in those who received captopril[18], 9.2 per cent in enalapril[19], and 8.3 per cent in benazepril[4]. In the present study, the prevalence of C-ACEI was 31.3 per cent when studied retrospectively and 23.6 per cent when studied prospectively which is much higher than that of many post marketing surveillance studies[13-16]. It showed that objective specific questions in the prospective study yielded a higher rate of C-ACEI than spontaneous reports of

Table 4. The prevalence of C-ACEI by the onset of cough and dosage.

Onset of cough (weeks)	Retrospective study						Prospective study					
	Low		High dose		Total		Low		High dose		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
1-4	40	38.5	34	45.3	74	41.3	21	50.0	14	42.4	35	46.7
5-8	17	16.4	13	17.3	30	16.8	9	21.4	6	18.2	15	20.0
9-12	15	14.4	7	9.3	22	12.3	7	16.7	8	24.2	15	20.0
13-16	13	12.5	7	9.3	20	11.2	3	7.1	3	9.1	6	8.0
17-20	13	12.5	9	12.0	22	12.3	2	4.8	1	3.0	3	4.0
21-24	5	4.8	3	4.0	8	4.5	0		1	3.0	1	1.3
> 24	1	1.0	2	2.7	3	1.7						
Total	104	100	75	100	179	100	42	100	33	100	75	100

n = number of cases

cough in the retrospective study (31.3% *vs* 23.6%, p = 0.02). The present study corresponded to that of Yeo et al which showed that spontaneous reports of cough would yield lower rates of responses when compared to the active participation in answering well designed questionnaires[20]. Therefore, the variability in the frequency of C-ACEI among reports is probably due to study methods.

The present study confirmed a remarkably high prevalence of C-ACEI among Asians. Higher prevalence of C-ACEI were previously reported among Chinese in Hong Kong i.e. 41.8 per cent for enalapril and 46 per cent for captopril[10]. In the Heart Outcomes Prevention Evaluation Study (HOPE), 340 of 4,645 patients (7.3%) aged 55 years or older discontinued ramipril due to the presence of cough. There were 1,035 cases who were initially excluded from the present trial partly due to adverse effects of the drug. It was reported that half of the patients who had C-ACEI preferred to discontinue the given medication [21,22]. Therefore, the prevalence of C-ACEI in the HOPE study should be higher than what was reported [7]. Moreover, in the Swedish Trial in Old Patients with Hypertension-2 study (STOP-2), cough was the most common reported adverse event in 11,048 ACEI treated patients (30.1%) aged between 70 and 84 years when the dropped out cases were included[12]. Similarly, in the present study, when 240 prospective studied patients were evaluated separately, the rate of C-ACEI (31.3%) was comparable to 30.1 per cent observed in the STOP-2 study in 1999 and 29.2 per cent reported by Singh et al in 1998[12,23].

The characteristics of cough observed in this study (Table 3) were similar to those reported previously. The prevalences of C-ACEI in both prospective and retrospective studies were unrelated to age [10,21,23]. Only in the retrospective study, a higher incidence of C-ACEI was noted among females compared to males (27.5% *vs* 16.9%, p = 0.001) (Table 1). This observation was comparable to those earlier reports[9,21,23-26]. The study on the frequency of C-ACEI in 1993 among 228 hypertensive patients in Greece by Efstrapoulos et al (125 females: 103 males) showed that 12 women and 3 men developed cough (p = 0.04)[25]. Singh et al also studied the prevalence of C-ACEI in 250 hypertensive patients and a higher frequency of C-ACEI was also observed among females compared to males (37.9% *vs* 15.5%, p < 0.001)[23]. On the contrary, the present prospective study suggested that C-ACEI had a trend to be related to gender (34.9% *vs* 25.3%, p = 0.12) (Table 1). This

might be explained by the small number of patients enrolled. However, a prospective study which systematically interviewed in a blinded manner using common adverse effect questionnaires reported by Woo et al on 191 hypertensive Chinese in Hong Kong showed that females and males had a comparable prevalence of C-ACEI[10].

Regarding the characteristics of cough, dry cough was observed in nearly all cases who had C-ACEI (93.8% from the retrospective study, 98.7% from the prospective study), similar to the previous study[23]. Cough frequently occurring at night was noted at the rate of 74.9 per cent, retrospectively and 80.0 per cent, prospectively which was comparable to 79.4 per cent reported by Singh et al[23]. Lastly, the onset of cough was commonly found within the first month of ACEI treatment (41.3% in retrospective and 46.7% in prospective studies), and gradually decreased thereafter. These observations agreed with that of Yesil et al in 1994[27].

Although some ACEI's were reported to produce cough less than others[27,28], the rates of C-ACEI in the present retrospective study were very high in every studied drugs (15.6-52.8%). There were no significant differences in the rates of cough induced by different ACEI's when compared with enalapril, except cilazapril and quinapril (52.8% *vs* 20.3%, $p < 0.0001$ and 35.4% *vs* 20.3%, $p = 0.002$, respectively) (Table 2). Remarkably, enalapril was the most frequently used drug in the present report (89.6% in the prospective study and 70.0% in the retrospective study). There were 2 reasons for the overwhelming usage of enalapril in the present study. Firstly, it was the only long acting ACEI to appear in the national drug list which was implemented a couple of years ago. Secondly, it was the only locally made drug available at that time. This left very few cases who used other ACEI's. Therefore, the rate of cough induced by other ACEI's could not reach any statistical significance when compared to enalapril. Similar findings were also found in the prospective study. Therefore, both cilazapril and quinapril might not be the only drugs which produced higher rates of cough than enalapril. However, the rate of enalapril induced cough was 20.3 per cent in the retrospective study and 30.7 per cent in the prospective study. Both figures were remarkably high.

It was usually said that only high dosages of ACEI induced cough. However, the present study was not designed to answer this question. It is common practice that every patient will be given a low dose of ACEI to start with and it will subsequently be titrated according to clinical responses. In the prospective study, the rate of C-ACEI appearing in the first 4 weeks was higher in the low dosage group than that of the high dosage group. This figure should be more reliable than the rate found in the retrospective study which showed the opposite (Table 4). It could be explained by the delay of spontaneous report of C-ACEI.

SUMMARY

In conclusion, the prevalence of cough induced by ACEI was higher than that of the post marketing surveillance reports. The onset of cough ranged from 1 to 32 weeks. Cough appeared to be more prevalent among females with disregard to age. It was irritative and nocturnal in nature, and commonly occurred within 4 weeks of treatment. The onset of C-ACEI was similar in both the low and high dosage groups. The rates of cough appeared to be very high in every studied drug.

ACKNOWLEDGEMENT

The authors wish to thank Professor Dr. Sathit Vannasaeng, Head of the Department of Research Promotion, Faculty of Medicine, Siriraj Hospital, for his valuable suggestions, and Mr. Suthipol Udompunthurak, Clinical Epidemiology Unit, Office for Research and Development, Department of Research Promotion, Faculty of Medicine, Siriraj Hospital, for his great help in the statistical analyses.

(Received for publication on March 18, 2003)

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ความชุกของการไอที่เกิดจากการใช้ยา Angiotensin converting enzyme inhibitor จากประสบการณ์ในโรงพยาบาลศิริราช

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อาการไอเป็นผลไม่พึงประสงค์ที่พบบ่อยจากการใช้ยากลุ่ม Angiotensin converting enzyme inhibitor (ACEI) ในการรักษาโรคความดันโลหิตสูงโดยเฉพาะอย่างยิ่งในผู้ป่วยเบาหวานและการรักษาโรคหัวใจล้มเหลว จากการศึกษาติดตามหลังยากลุ่มนี้ออกสู่ตลาดพบอุบัติการณ์ของการไอร้อยละ 0.1-4 อย่างไรก็ตาม การศึกษาในระยะหลังหลายรายงานพบอุบัติการณ์ของการไอมากกว่าที่รายงานไว้ก่อนหน้านี้มาก เพื่อศึกษาดูอุบัติการณ์และลักษณะของอาการไอที่เกิดจากการใช้ ACEI (C-ACEI) ในประชากรไทย จึงได้ทำการศึกษาแบบผสมระหว่างการศึกษาแบบ retrospective และ prospective ในผู้ป่วยที่มารับการรักษาที่แผนกผู้ป่วยนอก โรงพยาบาลศิริราชตั้งแต่เดือนธันวาคม 2542 ถึงเดือนสิงหาคม 2543 การศึกษานี้ทำในผู้ป่วย 1,000 รายที่เคยใช้หรือกำลังใช้ ACEI C-ACEI พบในผู้ป่วย 179 รายจาก 760 รายที่ศึกษาแบบ retrospective และ 75 รายจาก 240 รายที่ศึกษาแบบ prospective อาการไอเป็นชนิดระคายคอร้อยละ 93.8 จากการศึกษาแบบ retrospective และ ร้อยละ 98.7 จากการศึกษาแบบ prospective เป็นในเวลากลางคืนร้อยละ 74.9 จากการศึกษาแบบ retrospective และ ร้อยละ 80 จากการศึกษาแบบ prospective มักพบหลังการใช้ยาภายใน 4 สัปดาห์แรกร้อยละ 41.3 จากการศึกษาแบบ retrospective และ ร้อยละ 46.7 จากการศึกษาแบบ prospective ไม่พบความแตกต่างในอุบัติการณ์ของ C-ACEI ใน ACEI ชนิดต่าง ๆ ยกเว้น cilazapril และ quinapril ซึ่งพบมากกว่า enalapril จากการศึกษาแบบ retrospective ($p < 0.0001$ และ $p = 0.002$, ตามลำดับ) รูปแบบของการศึกษาจะมีผลต่ออุบัติการณ์ของ C-ACEI โดยพบว่าการศึกษาแบบ prospective จะมีอุบัติการณ์ของ C-ACEI สูงกว่าการศึกษาแบบ retrospective

คำสำคัญ : การไอ, ยายับยั้งเอ็นซัยม์เปลี่ยนแองจิโอเทนซิน

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จดหมายเหตุทางแพทย์ ฯ 2546; 86: 647-654

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