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High prevalence of persistent cough with angiotensin converting enzyme inhibitors in Chinese

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1 Angiotensin converting enzyme (ACE) inhibitors are in common use for the treatment of hypertension and heart failure. Whereas they are, in general, well tolerated, a dry cough can develop which, on occasion, requires termination of therapy. The reported prevalence of cough with ACE inhibitor therapy has varied from 0.2 to 25%, depending upon methods of data collection, analysis and symptom reporting.

2 To evaluate the prevalence of cough in Chinese patients receiving ACE inhibitors, interviews were carried out in 191 patients in Hong Kong who were taking therapy which included captopril or enalapril for hypertension or heart failure, and 382 patients matched for sex and age receiving alternative medications which excluded an ACE inhibitor (controls). Patients and controls were interviewed in a blinded manner by the same interviewer using a common adverse-effect questionnaire.

3 Persistent cough was reported in 44% of patients taking an ACE inhibitor (46% of those receiving captopril and 41.8% of patients taking enalapril), and in 11.1% of the controls ($P < 0.001$). The prevalence of other adverse reactions was similar, with no significant difference between the two treatment groups. The complication of cough was not related significantly to age, sex, underlying disease, drug dosage or smoking status.

4 This study indicates that cough is a common side effect of treatment with ACE inhibitors in Hong Kong Chinese, although in most patients cessation of therapy is not required. Whether Chinese are particularly susceptible to ACE-inhibitor cough requires a formal prospective study comparing Chinese and non-Chinese patients.

Keywords hypertension heart failure angiotensin converting enzyme inhibitors captopril enalapril cough Chinese

Introduction

Angiotensin converting enzyme (ACE) inhibitors are in common use for the treatment of hypertension and heart failure. They are, in general, well tolerated, but a dry irritating cough has been reported which, at times, requires cessation of therapy. The reported prevalence of cough has varied from 0.2 to 25% [1–7] depending on methods of data collection, analysis and symptom reporting [4–9].

Clinical observations in Hong Kong suggest a particularly high prevalence of cough associated with ACE inhibition in Chinese [10, 11], but objective information on this matter remains scanty. The purpose of the present study was to document the prevalence of cough in Chinese patients taking an ACE inhibitor for hypertension or heart failure.

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Methods

One hundred and ninety-one consecutive Hong Kong Chinese patients taking therapy which included enalapril or captopril were chosen at random over an 8-month period, and paired with 382 control patients taking alternative medications other than ACE inhibitors. Cases and controls were matched for age (within 5 years) and sex. All patients and controls were attending the hypertension or general cardiology clinic at the Prince of Wales Hospital in Hong Kong. Some of these patients (58%) have been enrolled in a study evaluating the racial difference of ACE inhibitor-induced cough between the Chinese in Hong Kong and Caucasians in Auckland [12].

Each patient was interviewed by the same observer who was unaware of drug therapy status. The patients were not aware that any one symptom (cough) was the focus of the interview. A common adverse effect and quality of life questionnaire with 26 items happening within 12 months prior to the interview, including the presence or absence of persistent cough, was used. Persistent cough was defined as a cough without identifiable cause persisting for more than 4 weeks. All other symptoms reported were similarly treated in detail and the interview has remained unbiased. Full details of drug therapy were recorded at the completion of the interview.

The statistical significance of differences between the two groups of patients was assessed by the chi-square test with Yates' correction. Differences were considered to be statistically significant at $P < 0.05$.

Results

Demographic data and details of drug therapy are shown in Table 1. Ninety-one patients in the ACE inhibitor group were receiving captopril and 100 patients took enalapril. Duration of ACE inhibitor therapy was 16.4 ± 4.7 (mean ± s.d.) months for patients on captopril, and 15.1 ± 3.8 months for those receiving enalapril. There was more hypertension and heart failure but less coronary disease in the ACE inhibitor group. A higher proportion of patients receiving an ACE inhibitor than controls were also taking diuretics or vasodilators, whereas the opposite was true for β-adrenoceptor blockers (Table 1).

The more frequently encountered adverse effects are shown in Table 2. Persistent cough was reported in 84 patients receiving an ACE inhibitor (44%, 95% confidence interval 36.8–51.3%) and in 42 controls (11%, 95% confidence interval 8.0–14.6%) (difference 33%, 95% confidence interval 25.3–40.7%) ($P < 0.001$). No other side effect approached the frequency of cough in patients taking ACE inhibitors (Table 2).

The prevalence of persistent cough was similar in patients receiving captopril or enalapril (46% and 41.8% respectively). Cough could not be related statistically to the patient's underlying disease, sex, age, history of cigarette smoking, or drug dosage (Table 3). In fact the mean daily dose of enalapril was lower in patients complaining of cough than in those without cough ($P < 0.05$).

Table 1 Clinical features

	ACE inhibitor patients (n = 191)	*Control patients* (n = 382)	P *value*
Age (mean ± s.d.)	56.8 ± 10.8	56.4 ± 11.3	
Sex			
Male	98	196	NS
Female	93	186	
Hypertension	111 (58.1%)	179 (46.9%)	< 0.02
Heart failure	51 (26.7%)	56 (14.7%)	< 0.001
Coronary disease	29 (15.2%)	95 (24.9%)	< 0.01
Arrhythmia		32 (8.4%)	
Others		20 (5.2%)	
ACE inhibitor:			
Captopril	100 (52.4%)	0	
Enalapril	91 (47.6%)	0	
Calcium antagonist	55 (23.6%)	113 (29.6%)	NS
β-adrenoceptor blocker	39 (20.4%)	157 (41.4%)	< 0.001
Diuretic	63 (33.0%)	81 (21.2%)	< 0.01
Vasodilator	52 (27.2%)	47 (12.3%)	< 0.001
Digoxin	31 (16.2%)	44 (11.5%)	NS
Nitrate	46 (24.1%)	92 (24.1%)	NS
Anticoagulant	39 (18.3%)	76 (19.9%)	NS
Others	35 (18.3%)	84 (22.0%)	NS

ACE: Angiotensin converting enzyme.

Table 2 Adverse effect/quality of life profiles

	ACE inhibitors	*Non ACE control*	P *value*
Skin rash	6 (3.1%)	16 (4.2%)	NS
Palpitation	17 (8.9%)	35 (9.2%)	NS
Cold extremities	7 (3.7%)	12 (3.1%)	NS
Urinary frequency	19 (10.0%)	51 (14.5%)	NS
Face flushing	5 (2.6%)	16 (4.2%)	NS
Blurred vision	8 (4.2%)	15 (3.9%)	NS
Dry mouth	15 (7.9%)	23 (6.0%)	NS
Constipation	13 (6.8%)	18 (4.7%)	NS
Numbness of muscles	25 (16.3%)	60 (15.7%)	NS
Muscle cramps	18 (9.4%)	43 (11.8%)	NS
Persistent cough	84 (44.0%)	42 (11.0%)	0.001
Nightmares	10 (5.2%)	19 (5.0%)	NS
General weakness	15 (7.9%)	26 (6.8%)	NS
Insomnia	23 (12.0%)	44 (11.5%)	NS
Poor thinking	5 (2.6%)	22 (5.8%)	NS
Poor memory	10 (5.2%)	28 (7.3%)	NS

NS: No statistical significance.

Most patients who complained of cough were able to continue taking captopril or enalapril. However, nine patients (9.9%) on enalapril and nine patients (9.0%) taking captopril stopped therapy because of cough.

Discussion

The reported prevalence of cough due to treatment with ACE inhibitors has varied greatly depending, in particular, on the method of data collection [5]. For example, cough attributed to enalapril has been noted in approximately 3% of patients from post-marketing

Table 3 Characteristics of patients with persistent cough while taking ACE inhibitors

	ACE inhibitor			
	Captopril	*Enalapril*	*Overall*	*Control*
Hypertension	29/62 (46.8%)	19/49 (38.8%)	48/111 (43.2%)	17/178 (9.6%)*
Heart failure	5/10 (50.0%)	18/41 (43.9%)	23/51 (45.0%)	7/56 (12.5%)*
Overall	46/100 (46.0%)	38/91 (41.8%)	84/191 (44.0%)	42/382 (11.1%)*
Male	21/42 (50.0%)	24/56 (42.9%)	45/98 (45.9%)	24/196 (12.2%)
Female	25/58 (43.1%)	14/35 (40.0%)	39/93 (41.9%)	18/186 (9.8%)
Age < 55 years	20/49 (40.8%)	16/39 (41.0%)	37/88 (42.0%)	
> 55 years	26/51 (51.0%)	22/52 (42.3%)	47/103 (45.6%)	
Smoker	3/8 (37.5%)	5/10 (50.0%)	8/18 (44.4%)	
Ex-smoker	3/5 (60.0%)	9/20 (45.0%)	12/25 (48.0%)	
Non-smoker	40/87 (46.0%)	24/61 (39.3%)	64/148 (43.5%)	
Drug dose (mg day^{-1})				
:No cough (mean ± s.d.)	35.0 ± 26.1	22.8 ± 12.9		
:With cough (mean ± s.d.)	41.1 ± 27.4	15.9 ± 9.3		
:*P* value	NS	< 0.05		

*Comparing with ACE inhibitors, $P < 0.001$.
( ) : Incidence of cough.
NS = No statistical significance.

surveillance studies and in 6–15% of subjects from hospital clinic surveys [7]. In the current study we found that 44% of patients taking captopril or enalapril had chronic cough compared with 11% in age and sex-matched patients receiving alternative forms of therapy. This is a higher prevalence of cough than reported hitherto, although Chan *et al.* documented cough from life-table analysis in 29% of Chinese patients starting an ACE inhibitor [11], and Town *et al.* documented new or aggravated cough in 31% of 80 patients taking captopril or enalapril [13].

When interpreting our results, there are potential limitations. First, our patients were not randomized prospectively to ACE inhibitor and control groups, thus the frequency of respiratory disorders, which could lead to cough, may not have been identical in the two groups. Any way, we have tried our best to identify and exclude those coughs related to an apparent respiratory disorder.

Second, it is possible that the true prevalence of cough with ACE inhibitors is underestimated. We presume that a certain percentage of patients would have developed cough of sufficient severity to warrant discontinuation of treatment and were hence included in our control (non-ACE inhibitor) group. In this regard, a prospective, life-table analysis in a large number of patients randomized to ACE inhibitor or non-ACE inhibitor treatment, might give a more accurate estimate of cough prevalence. Third, and on the contrary, it is conceivable that some patients taking ACE inhibitors were warned that cough is a potential complication of treatment. If so, then the prevalence rate we report might be excessive. Again, the true incidence or prevalence of this ACE inhibitor-induced complication will not be defined accurately until a careful, objective, prospective randomized study is performed in a substantial number of patients, none of whom are 'primed' to anticipate the possible development of cough. Such a theoretically ideal study may not be possible in practice.

The clinical impression is that Chinese patients may be more susceptible to ACE-inhibitor induced cough than other racial groups. Racial differences in pharmacokinetics and pharmacodynamics for ACE inhibitors might indeed exist – as has been demonstrated, for example, with propranolol [14]. The prevalence of ACE inhibitor-induced cough is not related to dose. In fact the dose of enalapril was lower in the cougher, which may be due to the dose having been lowered because of cough. It therefore seems very unlikely that the relatively low body weight in Chinese explains the difference in the prevalence of cough. It remains to be demonstrated, however, from formal studies in different races, that the Chinese are particularly prone to develop cough with ACE inhibitors. The very high prevalence of cough in controls and the similar prevalence in either sex would suggest a generally more sensitive cough reflex in the Chinese.

The majority of published reports suggest that ACE inhibitor-induced cough is reasonably well tolerated, may diminish in severity with time [15], and requires drug withdrawal in only a small percentage of cases. By contrast, Yeo & Ramsay found that cough severity forced cessation of therapy in 50% of patients who developed this symptom while taking enalapril [5]. Although only approximately 10% of our patients were withdrawn from treatment because of cough, this was not a formal prospective longitudinal study so the data may seriously underestimate true, long-term drug withdrawal rates.

Our study confirms the now well-established fact that ACE inhibitors can induce cough in patients with either hypertension or cardiac failure. The prevalence of cough appears especially high in Chinese patients, but formal comparative studies are required to define whether or not there are racial differences in susceptibility to ACE inhibitor-induced cough.

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