Effect of dose adjustment on enalapril-induced cough and the response to inhaled capsaicin

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- 1 In nine hypertensive patients with enalapril-induced cough the effect of altering the dose of enalapril on subjective cough and the cough response to inhaled capsaicin was examined in a random single-blind balanced cross-over study. They received three doses of enalapril, each for 3 weeks; the dose at entry (mean 10 mg daily); double this dose (mean 20 mg daily); and half this dose (mean 5 mg daily).
- 2 The cough response to inhaled capsaicin was also measured in two control groups: hypertensive patients on long-term enalapril treatment with no cough ($n = 18$), and hypertensive patients taking nifedipine ($n = 17$).
- 3 In patients with enalapril-induced cough there were significant dose-responses for enalapril as regards severity of cough ($P < 0.05$) and night time waking by cough ($P < 0.05$), but not for frequency of cough. Although the cough was less severe ($P < 0.02$) and caused less night time waking ($P < 0.03$) on the lowest dose of enalapril (mean 5 mg daily) it did not disappear completely in any patient.
- 4 The sensitivity to inhaled capsaicin did not differ significantly on the three doses of enalapril. The relative potency of capsaicin on enalapril 20 mg compared with enalapril 5 mg was 1.0 (95% CI 0.4–2.2). The wide confidence limits indicate that an important dose-dependent shift in capsaicin sensitivity is not excluded.
- 5 The sensitivity to inhaled capsaicin differed significantly between patients with enalapril-induced cough and both control groups. The relative potency of capsaicin was 0.2 (95% CI 0.1–0.4, $P < 0.001$) in patients taking nifedipine, and 0.4 (95% CI 0.2–0.8, $P < 0.005$) in patients taking enalapril who had no cough, when compared with patients with enalapril-induced cough.
- 6 The dose-response for capsaicin was shifted significantly to the left in patients on enalapril who had no cough when compared with patients taking nifedipine (relative potency 0.5, 95% CI 0.3–1.0, $P < 0.05$).
- 7 In patients with enalapril-induced cough reducing the dose improves the severity of cough and night time waking, but this may be of limited value as the cough persisted to some degree in all patients.
- 8 The enhanced sensitivity to capsaicin in patients taking enalapril who had no cough suggests that ACE inhibitors may alter the cough reflex in all patients, with those who develop cough representing the extreme of this general shift. This hypothesis needs to be tested in a larger prospective study.

Keywords enalapril cough capsaicin hypertension

Introduction

Persistent dry cough is the most common side-effect of ACE inhibitors [1], and the most frequent reason for stopping treatment [2, 3, 4]. It usually develops

within 4 weeks of starting treatment [5, 6], and is characteristically dry, repetitive, occurs in bouts which may cause vomiting, and is prominent at night

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[4]. In about a quarter of patients the cough is severe enough to require withdrawal of the ACE inhibitor, but most are able to continue on treatment [2, 4]. However among those who persist with treatment most consider their cough to be moderate or severe, and in the majority it disturbs sleep and is a nuisance to others [4]. The incidence of ACE inhibitor cough in controlled studies using validated methods of ascertainment is about 20% [4, 5, 7]. The cough is persistent, with a prevalence of 16% after 2 years of treatment [4] in addition to the 6% of patients who had stopped treatment because of cough [4]. Treatments such as non-steroidal anti-inflammatory drugs [8, 9], theophylline [10] or sodium cromoglycate [11] have not proved effective.

Sex and smoking habit are the only factors clearly related to development of ACE inhibitor cough, with cough reported twice as often by women [1, 2, 5, 12] and by non-smokers [12]. No clear relation has emerged between the dose of ACE inhibitor and development of cough [1, 2], but the effect of adjusting the dose of ACE inhibitor in patients with cough to determine whether there is a dose-response relationship has not been examined formally. Such a relationship might be important in managing patients with ACE inhibitor cough.

ACE inhibitor cough is probably mediated by C-fibres in the upper respiratory tract, as patients with this side-effect have increased sensitivity of the cough reflex to inhaled capsaicin, which acts specifically on C-fibres [13]. Patients with ACE inhibitor cough thus show a shift to the left of the dose-response to inhaled capsaicin [13, 14]. What is unclear is whether ACE inhibitor treatment shifts the capsaicin dose-response to the left *only* in those who develop cough as a side-effect [14], or whether there is a shift to the left in *all* treated patients [15] although only a minority develop cough.

The first aim of this study was to determine the effect of dose adjustment on the severity of enalapril-induced cough measured subjectively, and on the sensitivity to inhaled capsaicin. The second was to compare the capsaicin dose-response in hypertensive patients with enalapril-induced cough; in those treated with enalapril but without cough; and in those not taking an ACE inhibitor.

Methods

Patients

Nine hypertensive patients with enalapril-induced cough of a severity which did not require immediate interruption of treatment were recruited from the Sheffield Hypertension Clinic. The criteria for diagnosing ACE inhibitor cough were a new onset of persistent cough with no other identifiable cause, clinical criteria which have a positive predictive value of 95% for detecting ACE inhibitor cough [4]. The dose of enalapril at recruitment averaged 10 mg daily, with a range of 5–20 mg. Two control groups of hypertensive patients were recruited from the same clinic. One group ($n = 18$) had been treated with enalapril for a minimum of 9 months and on repeated direct questioning had not developed cough as a side-effect. The second control group ($n = 17$) had been treated with nifedipine, but no ACE inhibitor, for a minimum of 9 months. These three groups will be referred to as enalapril cough, enalapril control and nifedipine control, and their characteristics are shown in Table 1. All patients gave informed consent to the study which was approved by the hospital ethics committee.

Protocol

The nine patients with enalapril cough were randomised in a single-blind balanced cross-over study design to receive three doses of enalapril: their entry dose (mean 10 mg daily); double the entry dose (mean 20 mg daily); or half the entry dose (mean 5 mg daily). For example patients entering with cough on enalapril 20 mg daily were randomised to 10, 20 and 40 mg daily; and patients entering on 5 mg daily were randomised to 2.5, 5 and 10 mg daily. For convenience the mean dose levels (5, 10 and 20 mg) for the group will be cited in the results. Patients were blinded to the dosage of enalapril using opaque gelatin capsules. Treatment periods were of 3 weeks duration without formal washout intervals, but subjective scores were recorded only after the first week of treatment at the new dose was complete.

Table 1 Baseline characteristics of the enalapril cough group, and the two control groups used for the capsaicin cough response

	<i>Enalapril cough</i>	<i>Enalapril controls</i>	<i>Nifedipine controls</i>
Number of patients	9	18	17
Mean age (years)	58	58	60
(range)	(43–73)	(46–72)	(45–73)
Sex (% female)	67%	61%	59%
Enalapril dose (mg day ⁻¹)	10	24	—
(range)	(5–20)	(2.5–40)	
Smokers	22%	21%	27%

Subjective cough assessment

10 cm visual analogue scales (VAS) were used to measure the severity (cough mildest possible—cough worst possible) and frequency (coughed only once—coughed 24 h continuously) of cough. Patients also recorded the number of times per night they were wakened by cough. These measurements were entered in a diary record before retiring on each of the final 14 days of treatment phases, and the mean scores for the 14 days were calculated for analysis.

Capsaicin dose-response

This was measured by inhalation of single doses of capsaicin 0.05, 0.2, 0.8, and 3.2 nmol administered blind in random order via a handheld DeVilbiss No 40 nebuliser, with a 3 min interval between doses [16]. The number of coughs occurring in the first minute after each dose was recorded. Patients with enalapril cough had the capsaicin dose-response defined on three occasions, at 10.00 h on the final day of each treatment phase, and those in the two control groups had the capsaicin dose-response measured at 10.00 h on a single occasion.

Statistical analysis

The scores for severity and frequency of cough and night time waking by cough were analysed by the non-parametric Page test for ordered alternatives [17] to examine the significance of the enalapril dose-response, and Friedman's two way analysis of variance for differences between doses. The capsaicin dose-response curves were examined by analysis of variance appropriate to parallel line bioassay [18]. In each analysis the slopes (or common slope) were significant, and did not deviate from linearity or parallelism. The relative potency of capsaicin with 95% confidence intervals was calculated for the different experimental conditions. These relative potency estimates are a measure of shift of the capsaicin dose-response curve to left or right, with lower estimates indicating shift to the right and therefore reduced sensitivity to capsaicin. Correlations among

subjective and objective measures for cough were analysed by Spearman rank correlations (r_s).

Results

Comparability of groups

The three groups of patients were comparable as regards age, sex and smoking habit (Table 1). Patients with enalapril cough tended to be on smaller doses of enalapril than enalapril controls (mean 10 mg and 24 mg daily respectively, Table 1).

Enalapril dose and subjective cough

In the nine patients with enalapril-induced cough dose alteration from the initial mean dose of 10 mg daily to mean doses of 5 and 20 mg daily produced significant dose-responses for enalapril as regards severity of cough ($P < 0.05$) and night time waking by cough ($P < 0.05$), but not for frequency of cough (Page test; Table 2). Pairwise comparisons between the three dose levels of enalapril showed significant differences between the extreme dose levels (mean 20 mg vs mean 5 mg) for night time waking and cough severity (Table 2), with median values for episodes of night time waking 1.9 for enalapril 20 mg vs 1.1 for enalapril 5 mg ($P < 0.03$); and for cough severity 41 mm for 20 mg vs 23 mm for 5 mg ($P < 0.02$). In eight of the nine patients cough was more severe on the highest dose (mean 20 mg daily) than on the lowest dose (mean 5 mg daily). When compared with treatment with enalapril 20 mg daily, all nine patients had less frequent waking with enalapril 5 mg daily. However all nine patients continued to wake at night with cough on the lowest dose, indicating that the cough had not resolved completely.

Enalapril dose and capsaicin dose-response

The dose-response curves for capsaicin in the nine patients with cough on mean enalapril doses of 5, 10 and 20 mg are shown in Figure 1, and the relative

Table 2 Median values (and range) for cough severity and frequency by visual analogue scale (VAS), and episodes of night time waking by cough, in nine patients with enalapril-induced cough in a three-way crossover comparison of enalapril at mean doses of 5, 10 and 20 mg daily

	Mean enalapril dose			P values	
	5 mg	10 mg	20 mg	For trend	20 vs 5 mg
Cough severity (VAS mm)	23 (2–42)	27 (10–63)	41 (13–59)	< 0.05	< 0.02
Cough frequency (VAS mm)	23 (13–40)	46 (9–60)	29 (16–55)	NS	NS
Night time waking (per night)	1.1 (0.4–2.8)	2.7 (0.0–4.4)	1.9 (1.0–2.9)	< 0.05	< 0.03

Table 3 Relative potency estimates for capsaicin, with 95% CI, in (a) patients with enalapril-induced cough on mean enalapril doses of 5, 10 and 20 mg daily ($n = 9$); and (b) enalapril-treated controls ($n = 18$) and nifedipine-treated controls ($n = 17$) compared with the mean capsaicin dose-response in enalapril cough patients ($n = 9$)

Groups compared	Capsaicin relative potency	P
(a)		
Enalapril 10 mg vs Enalapril 5 mg	1.4 (95% CI 0.7–3.0)	NS
Enalapril 20 mg vs Enalapril 5 mg	1.0 (95% CI 0.4–2.2)	NS
Enalapril 20 mg vs Enalapril 10 mg	0.7 (95% CI 0.3–1.5)	NS
(b)		
Enalapril control vs Enalapril cough*	0.4 (95% CI 0.2–0.8)	< 0.005
Nifedipine control vs Enalapril cough*	0.2 (95% CI 0.1–0.4)	< 0.001
Nifedipine control vs Enalapril control	0.5 (95% CI 0.3–1.0)	< 0.05

*The mean capsaicin dose-response for three doses of enalapril (mean 5, 10 and 20 mg daily) was used in these comparisons.

Figure 1 Mean ($\pm$ s.e. mean) dose-response curves for nine patients with enalapril-induced cough while taking enalapril at mean doses of 5 mg ($\blacklozenge$), 10 mg ($\blacktriangledown$) and 20 mg ($\blacktriangle$) daily in a three-way crossover study. The slopes were significant ($P < 0.0001$) and did not deviate from parallelism ($P > 0.1$).

potency estimates and confidence intervals derived from these curves in Table 3. The three capsaicin dose-response curves overlapped and did not differ significantly. Pairwise comparisons of the capsaicin dose-responses on the three doses of enalapril showed that the relative potencies for capsaicin had confidence intervals bracketing unity, indicating that the potency of capsaicin did not alter significantly at different enalapril doses. The relative potency of capsaicin on high dose enalapril (mean 20 mg) vs low dose enalapril (mean 5 mg) was 1.0, with 95% CI 0.4–2.2. The upper confidence interval (2.2) indicates that the study had insufficient power to exclude an important shift to the left of the capsaicin dose-response with increasing doses of enalapril. The calculated responses to the geometric mean dose of capsaicin (0.4 nmol) were 4.3, 4.9, and 4.3 coughs min^{-1} on enalapril 5, 10 and 20 mg respectively.

Subjective cough vs capsaicin response

Correlations among the subjective measures of cough showed a high correlation between VAS scores for severity and frequency of cough ($r_s = 0.96$, $P < 0.0001$), but weak and non-significant correlations between these scores and night time waking with cough ($r_s = 0.57$ and 0.58 respectively). Subjective measures of cough showed no correlation with the responses to capsaicin as measured by the average cough response to capsaicin inhalation ($r_s = 0.27$, 0.20 , 0.31 for cough severity, frequency and waking respectively).

Capsaicin dose-response in enalapril cough vs control groups

For comparison with the two control groups the average capsaicin dose-response on the three doses of enalapril was used for the nine patients with enalapril cough. Figure 2 illustrates the mean dose-response in

Figure 2 Mean ($\pm$ s.e. mean) dose-response curves for patients with enalapril-induced cough ($n = 9$, $\blacklozenge$), enalapril-treated controls ($n = 18$, $\square$) and nifedipine-treated controls ($n = 17$, $\circ$). For patients with enalapril-induced cough the mean of the dose-response curves at three doses of enalapril (Figure 1) was used. The slopes were significant ($P < 0.001$) and did not deviate from parallelism ($P > 0.1$).

these nine patients and in the two control groups, and Table 3 shows the relative potencies of capsaicin calculated from these curves. There was a highly significant shift to the left of the dose-response for capsaicin in patients with cough when compared with both the enalapril and nifedipine control groups. Capsaicin had a potency of 0.2 (95% CI 0.1–0.4, $P < 0.001$) in nifedipine controls relative to enalapril cough patients, and a potency of 0.4 (95% CI 0.2–0.8, $P < 0.005$) in enalapril controls relative to enalapril cough patients. Direct comparison of the two control groups showed that the dose-response for capsaicin was shifted significantly to the left in enalapril controls (i.e. patients without cough) when compared with nifedipine controls ($P < 0.05$), so that capsaicin had a potency of 0.5 (95% CI 0.3–1.0) in nifedipine controls relative to enalapril controls (Figure 2, Table 3).

Discussion

Adjusting the dose of enalapril had a significant effect on the features of ACE inhibitor cough, with a significant dose-response relationship for enalapril as regards the severity of cough and episodes of waking at night. In broad terms reducing the dose of enalapril from 20 mg to 5 mg daily halved the severity of cough and the number of episodes of night time waking. However the results suggest that reducing the dose of ACE inhibitors may have somewhat limited value in ordinary practice. At the lowest dose of enalapril (mean 5 mg daily) the patients all continued to wake at night with cough, an indication that the cough had not resolved completely. It should be noted however that the duration of treatment phases was only 3 weeks, and further improvement may possibly occur with more prolonged dose-reduction.

The results confirm that the cough associated with ACE inhibitors is accompanied by increased sensitivity to inhaled capsaicin [13, 14], as shown by a significant shift to the left of the capsaicin dose-response curve in patients with cough compared with the two control groups without cough [13, 14]. However there was no evidence that adjusting the dose of enalapril had any effect on the dose-response curve for capsaicin, although the confidence intervals show that the number of patients studied was too small to exclude such an effect. There were no

significant correlations between the subjective measures of cough and the response to inhaled capsaicin. The apparent divergence of the findings for subjective cough assessment and capsaicin sensitivity could mean that they are measuring different things, but we think it more likely that it is caused by the variability in these endpoints. The capsaicin dose-response was measured on only a single occasion on each dose level, whereas the subjective responses represented the average of data collected over 14 days. Whatever the explanation it appears that repeated subjective measurements of cough are more discriminatory (and less unpleasant) than the response to inhaled capsaicin as a measure of ACE inhibitor cough.

The results for the two control groups treated with nifedipine or enalapril are of considerable interest. It is well established that patients with ACE inhibitor cough are more sensitive to inhaled capsaicin [13], implying that the cough is mediated by C-fibres. The situation prevailing in patients treated with ACE inhibitors who do not develop cough as a side-effect is less clear. In one study captopril appeared to shift the capsaicin dose-response curve to the left in all treated subjects [15] whereas in another ramipril appeared to shift the curve only in those who developed ACE inhibitor cough [14]. It is thus unclear whether ACE inhibitors tend to increase capsaicin sensitivity in all subjects, with those who develop cough representing the extreme of a general response; or whether ACE inhibitors increase capsaicin sensitivity only in the minority of patients who develop cough, implying an idiosyncratic or all-or-nothing response. In this study hypertensive patients treated with enalapril who had no cough had significantly enhanced sensitivity to inhaled capsaicin when compared with patients treated with nifedipine. This suggests that enalapril treatment may increase sensitivity to inhaled capsaicin in all patients, and that those who develop cough may lie at the extreme of a general shift in the cough reflex. It should however be noted that the difference between the two groups scarcely reached the conventional level of significance. Furthermore patients on nifedipine were selected as controls on the assumption that nifedipine has no effect on the capsaicin cough response—an assumption which has not been formally tested. The hypothesis that ACE inhibitors alter capsaicin sensitivity in all treated patients therefore needs to be tested in a placebo controlled study, and in a larger group of patients.

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