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Cough and enalapril: assessment by spontaneous reporting and visual analogue scale under double-blind conditions

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The incidence and prevalence of cough related to enalapril was assessed by spontaneous reporting and a visual analogue scale during a 6 month random double-blind parallel-group study comparing enalapril with nifedipine. Cough was reported spontaneously by 6.2% of enalapril-treated patients, and by none on nifedipine (NS). No patient had to discontinue enalapril because of cough. After 24 weeks treatment increases in visual analogue scale scores for cough frequency $\geq$ 8 mm were more common for enalapril than nifedipine (difference 21.5%, 95% CI 7.3–35.7%). Increased cough frequency by visual analogue scale was present throughout the study in women, but less consistently in men. High scores for cough were not related to the dose of enalapril. Cough with enalapril was not an important problem during the 6 months of treatment. However increased cough frequency could be detected by visual analogue scale, with a frequency consistent with that observed in open clinic-based studies of longer duration. These findings suggest that ACE inhibitor-induced cough may increase in severity over time, and that even a period of 6 months treatment is too short to evaluate this side-effect adequately.

Keywords enalapril cough visual analogue scales

Introduction

Persistent dry cough has emerged as an important side-effect of angiotensin-converting enzyme (ACE) inhibitors, and has been the commonest cause of drug withdrawal in some series (Gibson, 1989; Yeo & Ramsay, 1990). The incidence or prevalence of dry cough with ACE inhibitors depends greatly on the method of ascertainment (Yeo & Ramsay, 1990). Taking enalapril as an example, postmarketing surveillance studies have reported an incidence of about 3% (Coulter & Edwards, 1987; Inman *et al.*, 1988), whereas hospital clinic surveys have revealed a much higher incidence ranging from 6.3–14.6% (Gibson, 1989; Hood *et al.*, 1987; Strocchi *et al.*, 1989; Town *et al.*, 1987; Yeo & Ramsay, 1990). In a recent controlled hospital-based survey the prevalence of persistent cough during prolonged treatment with enalapril averaging 27 months was 15.9% higher (95% CI 7.2–24.6%) than that in matched nifedipine-treated patients (Yeo *et al.*, 1990). However cough has not been a prominent side-effect in blind prospective controlled trials of enalapril or other ACE inhibitors. This may reflect the small size or very short duration of many controlled trials, or a failure to recognise cough as a side-effect. On the other hand open studies reported from hospital clinics, many of which were uncontrolled, may have exaggerated the magnitude of the problem through over-reporting. We have examined in detail the incidence of cough in a 6 month double-blind controlled trial comparing enalapril with nifedipine (Maclean *et al.*, 1990), using spontaneous reporting and a visual analogue scale to measure the frequency of coughing. Our aim was to determine whether the findings in this controlled trial could be reconciled with those of surveys reported from ordinary clinical practice.

Methods

After a 2–4 week placebo run-in, 128 untreated hypertensive patients in three centres (74 men, 54 women; mean age 51, range 23–70 years; mean sitting blood pressure 160/105 mm Hg) were randomly allocated to treatment with enalapril (n = 65) or nifedipine retard (n = 63) and followed for 24 weeks in a double-blind parallel group study. Doses of these drugs were titrated as necessary over 8 weeks to control blood pressure, the dose of enalapril increasing from 5 mg to 40 mg daily, and that of nifedipine retard from 20 mg to 80 mg daily.

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After 8 weeks hydrochlorothiazide 12.5 mg daily, increasing to 50 mg daily if required, was added. The results for blood pressure and other variables have been reported fully elsewhere (Maclean *et al.*, 1990;). Possible side-effects were elicited at each visit by an open question 'have the tablets upset you in any way?' The frequency of coughing was assessed using a 10 cm visual analogue scale with the extremes marked 'I never cough' and 'I am always coughing'. This visual analogue scale was one of 16 scales administered, with the symptoms assessed chosen to provide balance as regards possible side-effects of enalapril and nifedipine. The visual analogue scales were administered before randomisation (pre-treatment), after 8 weeks (end of monotherapy), after 24 weeks (end of study), and if possible when patients withdrew from the study. The statistical methods used were the Kolmogorov-Smirnov two-sample test, chi-square with Yates correction, Fisher's exact test, and Wilcoxon rank sum test. One-tailed tests of significance are cited in view of the strong prior hypothesis that enalapril treatment, but not nifedipine treatment, would be associated with cough.

Results

Cough reported spontaneously

Twenty patients withdrew from the trial (6 enalapril, 14 nifedipine), 19 because of side-effects and one because of poor blood pressure control. In no case was cough the cause, or a contributory cause, of withdrawal. The upper 95% confidence interval for enalapril withdrawal because of cough within 24 weeks was 4.6% (the 95% CI for a rate of 0/65). Cough was reported in response to the open question by 4/65 (6.2%) patients treated with enalapril, and by none treated with nifedipine. This difference was not significant ($P = 0.06$, Fisher's exact test). The cough was non-productive, and its severity was graded as mild (1), moderate (2) or severe (1).

Cough by visual analogue scale

At 24 weeks 57 enalapril-treated and 48 nifedipine-treated patients remained on trial treatment, and had pre-treatment and 24 week visual analogue scale data. The pre-treatment visual analogue scale scores for cough frequency did not differ significantly between the enalapril and nifedipine groups. The daily doses of enalapril at 24 weeks were 10 mg ($n = 10$), 20 mg ($n = 5$), or 40 mg ($n = 42$).

The changes in mean score for cough over 24 weeks, + 1.3 mm for enalapril and −3.4 mm for nifedipine, did not differ significantly between treatments.

The distribution of changes from pre-treatment values at 24 weeks is shown for the two drugs in Figure 1. This showed an apparent excess of enalapril-treated patients with large increases in cough score, and the difference between the drugs in overall distribution approached significance ($\chi^2_{2df} = 4.81$, $P < 0.1$, Kolmogorov-Smirnov two-sample test). The critical point identified by the Kolmogorov-Smirnov test was an increase in cough score of 8 mm or more. Using this cut-off point those taking

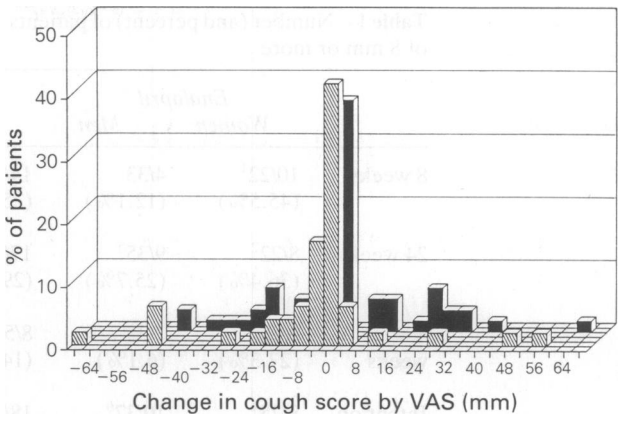

Figure 1 Distribution of changes in cough score from pre-treatment values after 24 weeks of treatment with enalapril (filled bars) or nifedipine (hatched bars).

enalapril had a significant excess of high scores at 24 weeks when compared with those on nifedipine (29.8% *vs* 8.3%; $\chi^2 = 6.24$, $P < 0.02$; difference 21.5%, 95% CI for difference 7.3–35.7%). The excess of high cough scores with enalapril was present in each of the three participating centres (26.7%, 24.2%, and 11.4%). The critical point identified by the Kolmogorov-Smirnov test, by definition, gives the maximal separation between treatments. However significant but smaller differences between enalapril and nifedipine were present when other cut-off points were chosen arbitrarily. For example the excess of high scores with enalapril was 16.3% at 10 mm or higher ($P < 0.05$), or 13.0% at 20 mm or higher ($P < 0.05$).

The increase in visual analogue scale cough frequency of 8 mm or more, defined in the Kolmogorov-Smirnov test, was used for further analysis. Table 1 shows data for 8 weeks of treatment, 8 and 24 weeks considered together, and an 'intention to treat' analysis which included the final visual analogue scale score for patients who withdrew. There was a high prevalence of increased cough score in women throughout, with an excess of 25.5% at 8 weeks and 23.1% at 24 weeks when compared with nifedipine-treated women. In men high cough scores on enalapril were not seen at 8 weeks, but were present at 24 weeks and in the intention to treat analysis (27.0% *vs* 5.7% in nifedipine-treated men; $\chi^2 = 4.45$, $P < 0.025$). After 8 weeks of enalapril treatment the prevalence of increased cough score was significantly higher in women (45.5%) than in men (12.1%; $P < 0.01$, Fisher's exact test), but there was little difference between the sexes at 24 weeks or in the intention to treat analysis (Table 1). Increases in score for cough frequency showed no relation to the dose of enalapril at 24 weeks. The prevalence of high cough scores was 31.0% in those taking enalapril 40 mg daily ($n = 42$) compared with 26.7% in those taking 10–20 mg daily ($n = 15$).

Discussion

Dry cough related to enalapril was not an important problem in this 6 month double-blind controlled trial. No patient had to discontinue enalapril because of cough within 6 months of starting the drug, despite treatment

Table 1 Number (and percent) of patients with increase in visual analogue scale score for cough of 8 mm or more

	Enalapril			*Nifedipine*		
	Women	*Men*	*Total*	*Women*	*Men*	*Total*
8 weeks	10/22[1] (45.5%)	4/33 (12.1%)	14/55 (25.5%)	3/15 (20.0%)	7/33 (21.2%)	10/48 (20.8%)
24 weeks	8/22[2] (36.4%)	9/35[5] (25.7%)	17/57[2] (29.8%)	2/15 (13.3%)	2/33 (6.1%)	4/48 (8.3%)
8 + 24 weeks	6/22[3] (27.3%)	2/33 (6.1%)	8/55 (14.5%)	1/15 (6.7%)	1/33 (3.0%)	2/48 (4.2%)
Intention to treat	8/25[4] (32.0%)	10/37[6] (27.0%)	18/62[2] (29.0%)	4/26 (15.4%)	2/35 (5.7%)	6/61 (9.8%)

[1] $P < 0.01$ *vs* men on enalapril; $P < 0.05$ *vs* total nifedipine.
[2] $P < 0.0125$ *vs* total nifedipine.
[3] $P < 0.0125$ *vs* total nifedipine; $P < 0.05$ *vs* men on enalapril.
[4] $P < 0.025$ *vs* total nifedipine.
[5] $P < 0.05$ *vs* total nifedipine.
[6] $P < 0.025$ *vs* men on nifedipine; $P < 0.05$ *vs* total nifedipine.

with the maximum dose of 40 mg daily in most patients. Few patients on enalapril complained spontaneously of cough, and there was no significant difference from nifedipine in this respect. These findings appear to contradict those in open and generally uncontrolled studies conducted in hospital clinics, and might suggest that clinic surveys have exaggerated the magnitude of the problem because of bias or over-reporting. In fact the results of the present study can be reconciled with those observed *within 6 months* in open clinic-based surveys. Cough was reported spontaneously by 6% of enalapril-treated patients in this study. This figure is identical to the 6% observed at 6 months in a life-table analysis of a cohort of patients started consecutively on enalapril (Yeo & Ramsay, 1990). No patient had to stop enalapril because of cough in the present study, but the confidence intervals for this zero incidence, 0–4.6%, bracket the withdrawal rate of 3.7% caused by cough within 6 months in the study cited (Yeo & Ramsay, 1990).

The frequency of cough was also assessed by a visual analogue scale in the present study. The mean scores for frequency of cough did not differ significantly between the enalapril and nifedipine groups, indicating that the scores did not shift in the population of enalapril-treated patients as a whole. However there did appear to be an upward shift of cough score in a minority of enalapril-treated patients (Figure 1). This difference between drugs in distribution of cough scores did not reach the conventional level of significance, and the findings for cough by visual analogue scale must therefore be regarded as hypotheses to be tested in further study. However using the cut-off point identified by the Kolmogorov-Smirnov analysis, 8 mm or higher, the results after 8 weeks treatment (Table 1) showed a consistent pattern, particularly in women. Further the excess in prevalence of cough with enalapril, when compared with nifedipine, was broadly similar to that reported in a clinic-based study which also used nifedipine as the control drug (Yeo *et al.*, 1990). These figures for prevalence of cough with enalapril in the present study and in the clinic-based study (Yeo *et al.*, 1990) were respectively, 21% and 16% in all patients, 23% and 23% in women, and 20% and 7% in men. The 20% prevalence of cough observed in men at 6 months in this study was considerably higher than that generally reported (Berkin & Ball, 1988; Just, 1989). In common with clinic-based studies (Gibson, 1989; Hood *et al.*, 1987; Strocchi *et al.*, 1989; Town *et al.*, 1987; Yeo & Ramsay, 1990) enalapril-induced cough was more common in women than men. This difference was large and statistically significant after 8 weeks treatment, but much less marked after 24 weeks. It is impossible to say whether this indicates a delayed onset of cough in men when compared with women, or whether it is simply a chance observation.

We believe that the key to the apparent discrepancy in the literature between controlled trials and clinic-based surveys of ACE inhibitor cough is the *duration* of treatment. The findings reported at 6 months in this double-blind controlled trial are consistent with observations at 6 months in the life-table analysis of clinic patients cited above (Yeo & Ramsay, 1990). In the life-table analysis the eventual incidence of self-reported cough was 14.6% (95% CI 10.2–19.0%) after 19 months of treatment, and the withdrawal rate because of cough reached 6.0% (95% CI 4.5–7.5%). An increased prevalence of cough could be detected after 8 and 24 weeks in the present study, particularly in women, but only by visual analogue scale. The implication is that the cough may increase in severity over time.

In summary, the findings for cough related to enalapril in this double-blind study are consistent with the results of previous clinic-based studies when duration of treatment is taken into account. Even 6 months duration of treatment appears too short to evaluate ACE inhibitor-induced cough adequately. Visual analogue scales appear to have some value in assessing cough, but this requires confirmation in further studies. Based on our experience in this study and in others (Yeo & Ramsay, 1990; Yeo *et al.*, 1990) we would recommend inclusion of visual analogue scales to measure the severity of cough and the presence of nocturnal cough, in addition to the scale measuring frequency of cough.

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