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Original article

Difference in incidence of cough induced by imidapril and ramipril: Role of prostaglandin synthesis inhibition

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ABSTRACT

Aim of this study was to evaluate whether treatment with imidapril reduced cough induced by ramipril. The effect of adding indomethacin, a known inhibitor of prostaglandin (PG) synthesis, to the two ACE-inhibitors (ACE-I) on cough frequency and intensity was also assessed. After a 2-week placebo period, 97 hypertensive patients who developed cough during ramipril treatment were randomized to ramipril 10 mg or imidapril 20 mg for 8 weeks. Thereafter, patients still complaining cough continued the respective ACE-inhibitor treatment, but in each arm they were allocated to receive also indomethacin 50 mg or placebo for 4 weeks according to a double-blind, cross-over design. At the end of each phase of the study cough was assessed by means of a self-administered questionnaire with an ordinal 10-point visual analogue scale for rating daily cough intensity and frequency. At the end of the 8-week monotherapy phase, cough was complained by 48 of 49 (98%) patients randomized to ramipril and by 24 of the 48 (50%) patients randomized to imidapril, the difference between the two groups being significant ($P < 0.01$). Indomethacin significantly reduced the mean score for cough intensity and frequency ($P < 0.01$) in both ramipril and imidapril treated patients, with no difference between the two groups. These results indicate that the incidence of cough recurrence is lower with imidapril than with ramipril. The finding that the effect of indomethacin on cough frequency and intensity is the same in the two treatment groups suggests that the lower incidence of cough observed with imidapril might be mediated by some mechanism independent of PG synthesis.

1. Introduction

Persistent dry cough is a common side effect of treatment with ACE-inhibitors (ACE-Is), with an incidence ranging from less than 1% to 35% [1–4]. Women, non-smokers, subjects with ACE genotype II and those of Asian and black ethnicity have been reported to develop more frequently ACE-inhibitor cough [5–9]. This side effect is often annoying and leads to discontinuation of therapy in many cases, representing the main cause of treatment withdrawal with ACE-Is [1,2,10].

The pathogenesis of cough induced by ACE-Is is still unclear. A possible mechanism is the accumulation of bradykinin in tissues as a consequence of inhibition of its metabolic breakdown by ACE-Is [2,4,11,12]. Increased levels of bradykinin in airway tissue might cause cough both directly, by sensitisation of vagal C-fibres and consequent enhancement of the cough reflex [13–15] and indirectly, through phospholipase A2 synthesis stimulation [16]. This latter activates the arachidonic acid pathway with consequent increase in prostaglandin (PGI2 and PGE2) synthesis [16]. PGs stimulate directly the rapidly adapting stretch receptors and pulmonary sensory C fibers, two components of the cough reflex [16,17]. This theory is supported by the finding that administration of indomethacin or sulindac, which are known to reduce PG synthesis by inhibiting the ciclooxygenase-controlled initial steps of the arachidonic acid cascade, produced a significant attenuation or disappearance of ACE-I cough in many patients [18–20]. Also picotamide and ozagrel, which inhibit the synthesis of thromboxane A2 (TXA2), another end-product of arachidonic acid metabolism, have been demonstrated to attenuate ACE-I cough, thus suggesting a role of TXA2 beside PGs in the development of this side effect [21,22]. Tachykinins such as substance P, a potent bronchoconstrictor, are also degraded by ACE. An increase in the substance P level due to decreased ACE activity is suspected as another possible mechanism of coughing with ACE-Is [11,23]. Evidence of this is provided by the observation that baclofen, a gamma aminobutyric acid agonist that inhibits substance P release, reduced ACE-I cough [24,25].

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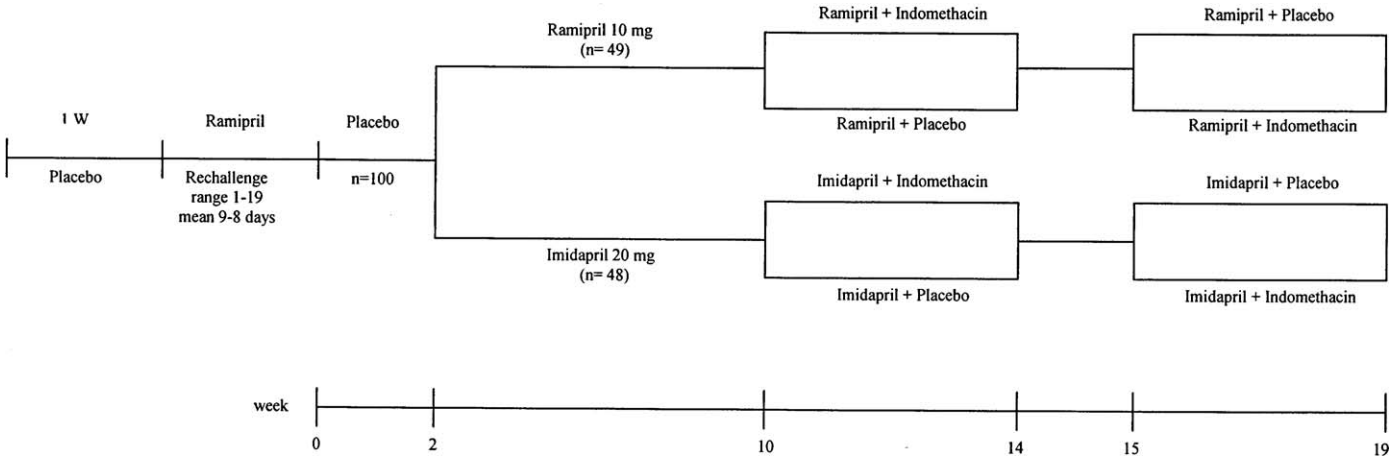

Fig. 1. Study design.

Although cough is considered a class-effect of ACE-Is, its actual incidence has been reported to vary among individual agents. In particular, some previous clinical studies have shown that the incidence of cough is lower with imidapril, a prodrug-type of ACE –I without a sulphydril (SH-) group, than with other ACE-Is [26–31].

The aim of the present study was to evaluate whether treatment with imidapril reduced cough induced by ramipril. The effect of adding indomethacin to the two ACE-Is on cough frequency and intensity was also assessed.

2. Patients and methods

Outpatients with mild to moderate essential hypertension (SBP > 140 < 165 mmHg and or DBP > 90 < 105) and identified in the previous 3 months as having ACE-inhibitor-induced cough were eligible for participation in the study. Patients receiving concomitant treatment with aspirin or nonsteroidal anti-inflammatory drugs were excluded from the study, as were patients with an airway disease or those who smoked.

All treatments were stopped for 1 week, and then ramipril 10 mg once daily was started. Patients were requested to return to the outpatient clinic after the reappearance of dry cough similar to that experienced before the withdrawal of all treatments.

At the end of the rechallenge period 100 patients who developed cough during ramipril treatment after 2 weeks of single-masked placebo treatment, were randomized to continue ramipril 10 mg or to shift to imidapril 20 mg for 8 weeks. Subsequently patients still complaining cough continued the respective ACE-inhibitor treatment, but in each arm they were allocated to receive also indomethacin 50 mg twice daily or placebo twice daily for 4 weeks according to a double masked, double-dummy, cross-over design (Fig. 1).

At the end of each phase, cough was assessed by means of a questionnaire completed by the patients, that contained an ordinal 10-point visual analogue scale (VAS) to score cough intensity and frequency during the daytime and by the following three questions assessing cough at night: (1) Did you have any difficult falling asleep last night due to coughing? (2) Were you awakened by coughing last night? And (3) If yes, how many times? Nighttime (11 p.m. to 7 a.m.) coughing was assessed in terms of the number of patients answering "yes" to questions 1 and 2 and in terms of the mean number of awakening episodes. To better assess coughing during the daytime (7 a.m. to 11 p.m.), three subperiods were considered: 9 a.m. to 5 p.m. (working hours), 5 p.m to 11 p.m. (evening hours), and 7 a.m. to 9 a.m. (trough hours). The mean rank coughing score was evaluated for each of the subperiods using the 10-point VAS.

At each visit, BP and HR were evaluated 24 hours after administration of medication. BP was measured by means of a standard mercury sphygmomanometer (diastolic BP, phase V of the Korotkoff sounds) in patients in the sitting position after a 10-minute rest. HR was measured by pulse palpation.

2.1. Statistical analysis

The statistical analysis of the data was performed by means of nonparametric tests to evaluate cough intensity and frequency (assessed by an ordinal scale) and parametric tests to evaluate the significance of observed differences between cardiovascular parameters. Nonparametric data are presented as mean ranks and intervals between the 25th and 75th percentiles. The BP and HR results are given as mean ± SD.

The differences between treatments during the same period were evaluated by the Wilcoxon signed-rank test with the Bonferroni adjustment. Differences were considered significant at the 5% level, when the Chi-square test showed $P \leq 0.016$. BP and HR differences were assessed using analysis of variance for paired data refined by the Student t test for paired comparison if significant results were obtained ($P < 0.05$).

3. Results

Ninety-seven outpatients (52 women, 45 men; age range 39 to 70 years) were enrolled in this study and were allocated randomly to ramipril 10 mg or imidapril 20 mg for 8 weeks: at the end of this monotherapy phase 48 of 49 (98%) patients randomized to ramipril complained cough, while among the patients randomized to imidapril cough was complained by 24 of the 48 patients (50%), the difference between the two groups being statistically significant ($P < 0.01$) (Table 1).

Indomethacin addition effect on daytime coughing evaluation was a significant reduction of the mean score for cough intensity and frequency ($P < 0.01$) both with imidapril and ramipril treatment without any difference between the two groups. Considering the three daytime subperiods, the VAS score of cough intensity and frequency was always similarly reduced in both treatment groups (Table 2).

With regard to indomethacin effect on nighttime coughing, no significant difference between treatments was noted in the percentage of patients having difficulty falling asleep due to coughing, which was similarly reduced. Also the number of patients who complained of awaking due to coughing and the mean number of waking episodes were similarly reduced in the two treating groups