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Original Article

Noscapine suppresses angiotensin converting enzyme inhibitors-induced cough

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SUMMARY:

Background: Dry cough is a common side-effect of the angiotensin converting enzyme inhibitors (ACEI) and is a major limiting factor of their use. It has been suggested that ACEI cause this side-effect by potentiation of the bradykinin effect. Previous work in our laboratory has shown that noscapine, an antitussive drug, inhibits the effect of bradykinin.

Methods: To investigate the effect of noscapine on ACEI-induced cough, 611 hypertensive patients who were being treated with ACEI were evaluated for the incidence of persistent dry cough.

Results: A cough had developed in 65 (10.6%) patients, two (3.1%) of whom also had severe respiratory distress that required hospitalisation and immediate discontinuation of the ACEI. Forty-two (64.6%) patients had developed a mild cough and 21 (32.3%) patients had developed a moderate to severe cough. The patients with moderate to severe cough received 15 mg of noscapine, orally three times daily, while they continued ACEI. Noscapine effectively resolved the cough in 19 (90%) patients within 4–9 days of starting treatment.

Conclusion: Noscapine, possibly by inhibition of bradykinin synthesis, eliminates ACEI-induced cough in the majority of patients and allows them to continue with ACEI therapy.

KEY WORDS: **angiotensin-converting enzyme inhibitor, cough, hypertension, noscapine.**

The angiotensin-converting enzyme inhibitors (ACEI) are among the most widely used medications in patients with cardiac and renal diseases. While they are generally well tolerated, their use has been limited due to their side-effects. They frequently induce a persistent dry cough, which has been reported in 5–39% of patients.[1–3] In most cases, the ACEI has to be discontinued because of this annoying side-effect.[1]

The mechanism of ACEI-induced dry cough has been attributed to bradykinin accumulation and/or the increment of prostaglandin synthesis associated with the use of ACEI.[4–7] Recent work in our laboratory on the contractile effects of bradykinin on the guinea pig ileum has shown that noscapine, an isoquinoline alkaloid found in opium,[8] is a non-competitive inhibitor of this peptide.[9] Unlike most other alkaloids obtained from the opium latex, this drug is devoid of any significant analgesic, sedative or euphoriant effects, which are commonly associated with this group of drugs. The only important and approved clinical effect of noscapine is its antitussive activity.[8] The experimental work with guinea pigs has shown that noscapine is very effective as an antitussive agent,[10] especially when cough is caused by bradykinin agonist FR190997 or ACEI, which inhibit the degradation of bradykinin.[11] The present work was carried out to investigate the effectiveness of noscapine in mitigating the dry cough induced by ACEI therapy.

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SUBJECTS AND METHODS

Formulation

Noscapine is formulated as compact 15 mg tablets. The direct compaction method is used to prevent any degradation of the drug due to moisture and heat. The main ingredients of the drug are gelatinised starch, polyvinylpyrrolidone (PVP), avicel, carboxymethyl cellulose (CMC) and magnesium stearate.

Patients and clinical protocol

In a period of one year, 611 Iranian hypertensive patients who were treated with ACEI were evaluated for the incidence of persistent dry

cough. Sixty-five patients (10.6%) had developed a cough. Among them, 42 (64.6%) patients had a mild cough, 21 (32.3%) patients had a moderate to severe cough and two (3.1%) patients had developed acute respiratory distress that necessitated the patients' admission to hospital and prompt discontinuation of the ACEI. We studied the effect of noscapine in the latter 21 patients, six men and 15 women, with a mean (±SD) age of 52.7 ± 2.2 years. ACEI-induced cough was defined as a dry cough that occurred after initiation of ACEI therapy, subsided within 7 days after discontinuation of the drug, and reappeared in 48–96 h after restarting the drug. Organic upper respiratory and pulmonary diseases were ruled out by physical examination and chest X-rays of the patients before restarting the ACEI. The characteristics of the patients are shown in Table 1. The Ethical Committee/Institutional Review Board of Rasool Akram Hospital approved the study and informed consent was obtained from all patients. The study was performed in the outpatient department of Rasool-Akram-Hospital, Iran University of Medical Sciences, Tehran, Iran.

Medication and evaluation

Patients filled a cough diary sheet during the initial 2 weeks of ACEI therapy. They were asked to score their cough severity according to the following scale: 0, no cough; 1, only a tickling sensation in the throat; 2, mild cough, which did not interfere with daily activities; 3, moderate cough, which interrupted some daily activities; and 4, severe cough, which persisted and interfered with most daily activities and disturbed sleep at night.

All patients with moderate to severe cough (3–4 score) were enrolled in the study and received noscapine 15 mg three times daily, while continuing with ACEI therapy. The dose of noscapine was at its recommended antitussive dose.[12]

During and after noscapine therapy, patients were asked to fill in a cough diary in a manner similar to the prenoscapine therapy period and continued taking noscapine until the severity of the cough was reduced and/or the cough resolved.

Statistical analysis

SPSS, version 11.5, was used for statistical analysis. Paired Student's *t*-test was used for comparison of the cough scores in the pre- and post-noscapine therapy periods. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

The characteristics of the patients who participated in this study are shown in Table 1. Seventeen (71%) of the patients were female. The mean (±SD) daily cough score was 3.8 (±0.09) before noscapine therapy and 0.4 (±0.3) at the final day of the treatment period, showing a significant reduction ($P < 0.0001$) in the cough score after the noscapine therapy. In the majority of patients (90%), a complete response was achieved within 3–10 days of noscapine therapy. Two of the patients did not respond to noscapine, which might suggest that an idiosyncratic reaction might be present in this response. Blood pressures were maintained around 110–130/70–80 mmHg, pre- and post-noscapine therapy, and interestingly, four patients required less antihypertensive medication during noscapine administration.

Table 1 Characteristics of patients who were treated with noscapine in the present study

No.	Gender	Age	Diagnosis	ACEI	Smoker	Cough severity	No. days to initial response	No. days to complete response
1	M	28	GN/HTN	Enalapril	–	4	3	5
2	M	61	HTN	Enalapril	+	3	2	4
3	F	51	HTN	Enalapril	–	4	–	–
4	F	69	HTN/Hypothy	Enalapril	–	3	3	5
5	F	44	HTN	Enalapril	–	4	4	6
6	F	42	HTN	Enalapril	–	4	3	5
7	F	55	HTN	Enalapril	–	4	3	5
8	F	41	Hypothy/MGN HTN	Enalapril	–	4	4	6
9	F	57	HTN	Enalapril	–	3	3	5
10	F	51	HTN/DN	Captopril	–	4	–	–
11	M	50	DN/HTN	Enalapril	–	3	3	5
12	F	60	DN/HTN	Captopril	–	4	4	7
13	F	48	HTN	Enalapril	–	4	3	5
14	F	54	HTN	Enalapril	–	4	3	7
15	M	55	DN	Captopril	–	4	4	7
16	M	71	DN/HTN	Captopril	–	4	2	4
17	F	50	DN/HTN/CHF	Captopril	–	4	2	7
18	F	54	DN/HTN	Captopril	–	4	2	8
19	F	52	DN	Enalapril	–	4	2	4
20	M	60	HTN	Enalapril	–	4	2	3
21	F	48	HTN	Enalapril	–	4	6	10

P-value of cough scores between pre- and post-noscapine therapy was statistically significant ($P < 0.0001$).

ACEI, angiotensin converting enzyme inhibitor; CHF, congestive heart failure; DN, diabetic nephropathy; F, female; GN, glomerulonephritis; HTN, hypertension; Hypothy, hypothyroidism; M, male; MGN, membranous glomerulopathy.

DISCUSSION

Dry cough is the most common side-effect associated with ACEI therapy, and is a major limiting factor in terms of continuing the medication.[1–3] We found an incidence of 10.6% among the patients in the present study, which is within the range of 5–39% reported in the literature.[1–3] Similar to other groups, we found that the frequency of cough is higher in women and non-smokers.[13,14] Interestingly, a much higher incidence of persistent ACEI-induced cough has been reported in Asians (Chinese patients in Hong Kong), as compared with Caucasians, 53% versus 18%, respectively, raising the possibility of racial differences in the susceptibility to this adverse effect.[15]

Various mechanisms have been implicated in the pathogenesis of this side-effect. Bradykinin, prostaglandins and nitric oxide (NO) are the most frequently proposed causes of ACEI-induced cough.[1–4,16–19] Bradykinin has both direct and indirect effects on the airways, which includes bronchoconstriction, bronchodilation, stimulation of cholinergic and sensory nerves, increasing mucous secretion, inducing cough, and bronchial oedema due to capillary leakage.[17] Nitric oxide is released from cholinergic, sensory and nonadrenergic non-cholinergic nerves.[18] Bradykinin has three receptors: B1, B2 and B3. The airway effects are mediated predominantly by the B2 receptor subtype.[19] Several studies have used non-steroidal anti-inflammatory drugs, such as sulindac and indomethacin, to abolish this side-effect without any significant benefit.[1–5] Ebrahimi *et al.* showed that FR190976 (a bradykinin agonist) similar to ACEI could potentiate cough reflexes.[10] The present study shows that noscapine, a bradykinin antagonist, could effectively suppress cough in patients treated with ACEI.[9] This further supports the involvement of bradykinin in ACEI-induced cough reflexes. Interestingly, there was no change in blood pressure pre- and post-noscapine therapy, and four patients required less antihypertensive medications during noscapine administration. This finding was of interest because the antihypertensive effect of ACEI is believed to be at least in part mediated by bradykinin, which was supposedly blocked by noscapine. The current results are of interest for patients who develop this side-effect but need continued therapy with ACEI for the management of cardiovascular or renal problems, although angiotensin receptor blockers can often be safely substituted for ACEI.

Ferrous sulphate has also been shown to reduce ACEI-induced cough, presumably through inhibition of nitric oxide synthesis.[16] However, while ferrous sulphate therapy had only reduced the severity of ACEI-induced cough, noscapine could eliminate the cough altogether in the vast majority of patients. However, because cough is a very subjective symptom and the cough score depended on self-reporting, the open labelled design of the present study constitutes a weakness that should be resolved in the future by prospective, randomised, double-blinded studies.

In conclusion, noscapine can be used in the management of ACEI-induced cough, which would allow continuation of ACEI therapy. The present findings support the idea that bradykinin is involved in the induction of cough reflexes associated with ACEI therapy.

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