

The Effect of Aspirin on Converting Enzyme Inhibitors-Induced Coughs: A Double -Blind Clinical Trial

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Abstract

Background- Dry coughs are the most common adverse effect and limiting factor of all angiotensin converting-enzyme inhibitors (ACEI). Prostaglandins have been pinpointed as playing an important role in the genesis of this problem. This double blind clinical trial was designed to compare the efficacy of 500 miligram(mg) aspirin versus placebo in controlling ACEI-induced coughs.

Methods-The subjects were 32 patients, who had developed ACEI-induced coughs. They were randomized to a daily dose of 500 mg aspirin or placebo for a treatment period of 4 weeks. The means of cough severity before and each week for 4 weeks were compared in the two groups.

Results- Means of cough severity in the aspirin and placebo groups before and at the end of the first week of treatment did not show any significant difference. After the second, third and fourth weeks, the cough severity score was significantly reduced in the aspirin group ($p < 0.001$).

Conclusion- 500mg aspirin once daily can suppress or abolish ACEI-induced coughs, and this finding proposes alternative therapeutic approaches for ACEI-related coughs (*Iranian Heart Journal 2005; 6 (1,2): 17-19*).

Key words: aspirin ■ coughs ■ angiotensin-converting enzyme inhibitor

The angiotensin-converting enzyme inhibitors (ACEI) are the most widely used drugs in the field of cardiovascular medicine.¹

ACEI may be the first line drugs for diabetics patients with hypertension, in valvular regurgitations, systolic left ventricular dysfunction, diabetic nephropathy and among post-infarction patients.²

Dry bothersome coughs are the most common adverse effect of all ACEIs. This side effect has been reported to occur in 5% to 39% of patients treated with ACEI; in most cases, the drug has to be discontinued.³

Coughs occur substantially more frequently in women than in men.⁴

The mechanism that induces ACEI-induced dry coughs has not been fully elucidated. Increment of prostaglandin(PG) or bradykinin accumulation and substance P have been reported to be responsible for this side effect.⁵⁻⁶

PGs have been suggested to play a leading role in the genesis of ACEI-associated coughs.⁵ Non steroidal anti-inflammatory drugs (NSAIDs) and thromboxane antagonists resulted in the attenuation or disappearance of ACEI coughs.⁷⁻⁸ The role of different doses of aspirin in ACEI-induced coughs was not elucidated. The present double-blinded clinical trial was aimed at determining whether 500mg aspirin daily can control ACEI-induced coughs.

Methods

The subjects were 32 patients, who had developed dry coughs while taking ACEI. They were comprised of 8 men and 24 women, whose mean age was 59.1 ± 8.4 years. Evidence of organic pulmonary diseases was ruled out by physical examination and chest x-rays in each of the patients. There was no significant difference in the clinical characteristics between the treatment and placebo groups. After an informed consent had been obtained, the cough severity scoring according to the following scale was done: 0=no coughs; 1, only a tickling sensation on the throat; 2=mild coughs, isolated coughs; 3=moderate coughs, tolerated but severe enough to interrupt daily activities for some time; and 4=severe coughs, persisting and interfering with most of the daily activities or disturbing sleep at night. They were randomized to either the aspirin group, which received 500mg once daily as a tablet or a placebo group. Randomization was arranged, and neither the patient who took the drug nor the physician who prescribed it was aware of which group he or she belonged to. Over the 4 weeks' treatment period, the patients were asked to mark a self-administered questionnaire; at the end of each week, the patients were visited by physician. The mean of cough severity score for each week in the two groups was calculated and compared. Data were expressed as mean±SD. For comparing and analyzing cough severity in the two groups, independent T-test was used. Severity of coughs in each group before and after treatment was analyzed by paired T test. A value of $p < 0.05$ was considered significant.

Results

In this study, 32 subjects were divided into two groups; in each group, 12 males and 4

females were evaluated. Mean age of the aspirin group subjects was 57.5 ± 8.5 , and in the placebo group it was 60.6 ± 8.4 years (Table I).

Table I: baseline characteristics of patients

VARIABLES	ASPIRIN GROUP	PLACEBO GROUP
Age(Mean±SD)	57.5 ± 8.5	60.6 ± 8.4
Male	4	4
Female	12	12

The mean cough severity score before the treatment period in the aspirin group and placebo group was 2.44 ± 0.22 and 2.5 ± 0.16 , respectively, showing insignificant difference ($P < 0.821$). At the end of the first week after treatment, the cough severity score remained insignificant between the two groups ($p < 0.542$). After the second, third and fourth weeks after treatment, cough severity in the aspirin group was 1.31 ± 0.12 , 0.75 ± 0.14 and 0.63 ± 0.13 ; in the placebo group, however, it was 2.5 ± 0.11 , 2.38 ± 0.18 and 2.31 ± 0.20 , which showed reduction in the cough score throughout the treatment period in the aspirin group. A comparison between these findings and those of the placebo group showed a statistically significant difference between the two groups in all the three measurements ($p = 0.0015$, Table II).

Table II: mean of cough severity before and during treatment period (sg=significance).

Treatment Period	Cough Score (Mean±Sd)		p-value
	ASPIRIN GROUP	PLACEBO GROUP	
Before treatment	2.44 ± 0.22	2.50 ± 0.16	0.821
First week	1.94 ± 0.11	2.06 ± 0.17	0.542
Second week	1.31 ± 0.12	2.25 ± 0.11	0.0015 sg
Third week	0.75 ± 0.14	2.38 ± 0.18	0.0015 sg
Fourth week	0.63 ± 0.13	2.31 ± 0.20	0.0015 sg
Total after treatment	1.03 ± 0.11	2.21 ± 0.13	0.0015 sg

Discussion

Although dry coughs are the most often reported and annoying complication associated with ACEI use, their mechanism remains to be clarified. The incidence of ACEI-induced coughs ranges from 5% to 39%, but it is evident that the coughs are a major limitation of continuing the medication.³

The main finding of our study was that aspirin in a dose of 500mg once daily reduced or completely abolished coughing. Although several mechanisms have been proposed, none completely explain how ACEI produce coughs. Bradykinin and prostaglandins are the most frequently proposed causes of coughs^{5,6} and many studies using nonsteroidal anti-inflammatory drugs (NSAID), such as sulindac and indomethacin, have been undertaken to attempt to abolish this side effect and thus continue medication.^{9,10} Aspirin can inhibit the production of both prostacyclin (vasodilator and antithrombotic) and thromboxanes.² There are few clinical reports regarding the role of different doses of aspirin in cough modification. Low doses of aspirin were ineffective to suppress ACEI-induced coughs; like our study, 500mg aspirin favorably modified the cough severity score in the case group.² In conclusion, 500mg aspirin daily successfully diminishes ACEI-induced coughs, and this fact supports the hypothesis that ACEI-induced coughs may be associated with excessive generation of bradykinin and PGs. We suggest that patients who have to take ACEI and suffer from dry coughs should be prescribed 500mg aspirin once daily.

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