

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

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ABSTRACT

Background: Dry cough is the most common adverse effect and limiting factor of all angiotensin converting-enzyme inhibitors (ACEIs) . Prostaglandins have been pinpointed as playing an important role in the genesis of this problem. This double blind clinical trial desinged to study the efficacy of 500 milligram(mg) of aspirin comparing with placebo in controlling Enalapril-induced cough.

Methods: The subjects were 32 patients who had developed Enalapril-induced cough.They were randomized into two groups: a group of daily dose of aspirin, 500 mg and a group of placebo for a treatment period of 4 weeks. Mean of cough severity was compared between two groups before treatment and weekly, until 4 weeks.

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

Conclusion: 500mg aspirin, once daily, can suppress or abolish Enalapril-induced cough and this finding proposes alternative therapeutic approach for ACEIs-induced related cough.

Keywords: aspirin, cough, Angiotensin-Converting Enzyme Inhibitors (ACEIs), enalapril

Angiotensin-converting enzyme inhibitors (ACEIs) are the most widely used drugs in the field of cardiovascular medicine¹. ACEIs may be used as the first line drugs for treatment of hypertension in diabetic patients, valvular regurgitations, systolic left ventricular dysfunction, diabetic nephropathy and post infarction patients². Dry bothersome cough is the most common adverse effect of all ACEIs. This side effect has been reported to occur in 5% to 39% of patients who have been treated with ACEIs and in most cases, the drug must be discontinued³.

Cough tends to occur more frequently in women rather than men⁴. The mechanism of ACEIs-induced dry cough has not been fully elucidated. Increase of prostaglandin (PG) production, bradykinin and substance P accumulation; have been reported to be responsible for this side effect^{5,6}.

PGs have been suggested to play a leading role in the development of ACEIs-induced cough⁵. Non steroidal anti-inflammatory drugs (NSAIDs) and thromboxane antagonists result in attenuation or disappearance of ACEIs-induced cough^{7,8}. The role of different doses of aspirin in controlling ACEIs-

induced cough is not yet elucidated. The present double-blind clinical trial was aimed to determine whether aspirin, 500 mg daily could control ACEIs-induced cough.

Subjects and Methods:

The subjects were 37 consecutive patients who had been referred to cardiology clinic and had developed dry cough while taking enalapril. Five participants were excluded because of our exclusion criteria: asthma, chronic lung disease, sinusitis, and esophageal reflux and finally 32 patients remained in the study. Organic pulmonary diseases, sinusitis, and esophageal reflux were ruled out by history taking, physical examination, and chest x-ray in each patient. The patients included 8 men and 24 women with mean age of 59.1 ± 8.4 years old. There was no significant difference in clinical characteristics of the aspirin and placebo groups. After that an informed consent was obtained, the cough severity was scored according to the following scale: 0=no cough, 1= only a tickling sensation in the throat, 2=mild, isolated cough, 3=moderate cough, which was tolerated but was severe enough to interrupt daily

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activities for some time, and 4=severe cough, which persisted and interfered with most of the daily activities, or disturbed night sleep.

The patients were allocated to either aspirin group, which received 500mg of aspirin, as a micro-coated tablet once daily or placebo group. The placebo and aspirin tablets produced by the same company and they were similar in the shape and color. We used stratified allocation according to gender. The study was designed as double blind and neither the patients taking drug nor the physician prescribing it, were aware of the group who were belonged to it. During the four-week of treatment period patients were asked to mark on a self-administered questionnaire and at the end of each week the patients were also visited by the physician. In two groups median cough severity score for each week were calculated and compared.

Sample and statistical analysis

According to $\alpha=0.05$ and $\beta=0.20$ and effect size (difference between two means) equal to standard deviation (standard effect size =1), sample size was calculated as 16 patients in each groups.

Data are expressed as median. For comparing and analyzing cough severity in two groups Mann whitney test was used. A value of $p<0.05$ was considered significant.

Results

In this study 32 subjects were divided into two groups and in each group 12 males and 4 females were evaluated. Mean age of aspirin group subjects were 57.5 ± 8.5 and in placebo group were 60.6 ± 8.4 years old.

The cough severity score before treatment period in aspirin group and placebo group didn't show significant difference. At the end of the first week of

treatment, cough severity score difference remained non significant between two groups. After the second, third, and fourth weeks of treatment, cough severity score was reduced significantly in aspirin group in comparison to placebo group during this period (table 1).

Discussion

The main finding of our study was that aspirin with dose of 500mg, once daily, reduced coughing or completely abolished it. Although several mechanisms have been proposed, none of them completely explains how ACEIs may cause cough. Bradykinin and prostaglandins are the most frequently proposed causes for the cough^{5,6}. Many studies, have used nonsteroidal anti-inflammatory drugs (NSAIDs) such as sulindac and indomethacin attempting to abolish this side effect and thus enabling the patients to continue medication^{9,10}. Aspirin can inhibit production of both prostacyclin (vasodilator and antithrombotic) and thromboxanes². There are a few clinical reports regarding the role of different doses of aspirin in cough modification. Low dose of aspirin (100mg daily) was ineffective to suppress ACEIs-induced cough, but aspirin, 500mg daily, favorably decreased cough severity score in case group just like our study². Both aspirin and ACEIs are often used concomitantly, especially in patients with hypertension, heart failure, and ischemic heart disease. The safety of this treatment protocol has been a question because both of these drugs affect prostaglandin-mediated pathways. Combined treatment by low dose aspirin and ACEIs seems to be safe and useful^{11,12,13}. About the use of doses higher than 100mg of aspirin in patients who receiving ACEIs conflicting results have been reported in the literature.

Table1. Median of cough severity score before and during the treatment period.

TREATMENT PERIOD	COUGH SEVERITY SCORE				P-value
	ASPIRIN GROUP		PLACEBO GROUP		
	Median	Mean Rank	Median	Mean Rank	
Before treatment	2	16.16	2	16.84	0.828
First week	2	15.66	2	17.34	0.616
Second week	1	10.38	2	22.63	0.0015 *
Third week	1	9.16	2	23.84	0.0015 *
Fourth week	1	9.13	2	23.88	0.0015 *
Total after treatment	1.25	8.78	2	24.22	0.0015 *

* = P-value<0.05

There is some explanation for these conflicting results:

differences in study design, differences in the choice of the evaluation parameter, differences in the characteristics of the patients (different underlying disease, e.g. heart failure, hypertension or ischemic heart disease), and differences in the type and the dosage of each treatment (especially ACEIs and aspirin), thus further studies are needed to examine the exact mechanism of the interaction between aspirin and ACEIs¹⁷. However many studies concluded no important interaction between them^{2,14,15,16}. For example in patients with diagnosis of heart failure, the use of aspirin, in combination with

ACEIs, does not worsen long-term survival compared to the use of ACEIs lonely¹⁶.

In conclusion, 500mg of aspirin, once daily, successfully diminishes ACEIs-induced cough and this fact supports the hypothesis that ACEI-induced cough may be associated with excessive generation of bradykinin and PGs. We suggest prescribing aspirin, 500mg once daily, in patients who have to use ACEIs and have dry cough as a side effect.

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