

Effect of *Althaea Officinalis* on Cough Associated with ACE Inhibitors

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Abstract: Nowadays Angiotensin- converting enzyme inhibitor drugs are the leading drugs for the treatment of hypertension, heart failure and some of nephropathy. But One of the most frequent side effect of these drugs is cough. A dry, tickly and often bothersome cough that may develop in around 15 to 39 percent of these patients and may lead to discontinuation of treatment. So we decided to use herbal drug of *althaea officinalis* for the treatment of this cough. For this study in the year 1385 and by using of method of double-blind clinical trial 60 patients with hypertension who were from the province of Chaharmal va bakhtiarei and had been developed cough during taking of angiotensin - converting enzyme inhibitor drugs were selected. Then for all of them were filled a paper of questionnaire. In these papers the scores of severity of their cough on a scale between 0 to 4 and the advantages of their spirometry tests were noted. Then all of these patients were divided in 2 groups. The first group was treated by herbal drug of *althaea officinalis* and the second group by placebo by 20 drops for every 8 hour (TDS). These patients used these drugs for treatment period of 4 weeks. At the end of 4 weeks the scores of severity of their cough with the advantages of their spirometry tests were noted again. The Mean scores of the severity of the cough in the first group which have been treated by *althaea officinalis* had a significant change from the score of) 2/66+0.958 (to) 1/23+1.006 (Eight patient in the *althaea officinalis* group showed almost complete cough abolition. No significant change in laboratory data related to spirometry tests were observed in either group. The mechanism of this type of cough maybe is related to the stimulation of tracheae-bronchial tree and the herbal drug of *althaea officinalis* can have important role in decreasing and treatment of the cough of ACEI drugs.

Key words: Angiotensin, converting enzyme inhibitor drugs (ACEI), cough, *althaea officinalis*

Introduction

ACE inhibitors are valuable and effective drugs in the treatment of hypertension, heart failure, myocardial infarction and nephropathy. They are generally well-tolerated, but persistent dry cough has been occur in 5% to 39% of patients (Sebastian *et al.*, 1991).

The mechanism that induces ACE inhibitor-induced dry cough has not yet been fully elucidated.

ACE inhibitor-induced cough appeared to occur through the accumulation of substance P or bradykinin in the respiratory tract and subsequent stimulation of the cough reflex pathway (Morice *et al.*, 1987; Gilchrist *et al.*, 1989; Fox *et al.*, 1996).

Other reports have proposed that ACEI cause an increase in No generation. No is known to have inflammatory effects on bronchial epithelial cells (Linz *et al.*, 1999; Flak and Goldman, 1996; Sang *et al.*, 2001). Marshmallow is a very useful household medicinal herb. It's soothing demulcent properties make it very effective in treating inflammations and irritations of the mucous membranes such as the respiratory organs. The whole plant, but especially the root, is antitussive.

The root contains about 37% starch, 11% mucilage 11% pectin. *Althaea* root's mucilage content relieves dryness and irritation in the chest and throat (Faccila, 1990).

We sought to determine effect of *Althaea officialis* on cough Associated with ACE inhibitors in hypertensive patients.

Materials and Methods

Subjects: The subjects were 63 Iranian patients who had developed dry cough while taking ACEI for primary Hypertension. They included 18 men and 45 women. None of these patients had experienced symptoms of upper respiratory tract infection for >4 weeks before enrollment. Exclusion criteria were secondary or malignant hypertension, and cardiovascular, liver, or renal diseases. There was no significant difference in sex, age, mean of using dose ACEI, duration of taking ACEI Severity of cough and spirometry findings. All subjects gave informed consent, and the study was approved by the ethical committee of the Shahrekord Medical University.

Randomization and intervention: For all patients spirometry was performed before and after intervention. The spirometric device was Schiller version 1.5 predict 1998 Crapo ATS. They were randomized to either an Altho-cough group, which received 40mg of *Althaea officinalis* three daily as 20 drops, or a placebo group.

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Table 1: Change in cough scores with Althaea officinalis

| Groups | Cough Scores (Mean ± SD) |
|------------------|--------------------------|
| Althaea | |
| Before treatment | 2.66±0.95* |
| After treatment | 1.23±1* |
| Placebo | |
| Before treatment | 2.7±0.79 |
| After treatment | 2.33±0.84 |

* P< 0.05 between before and after treatment

Table 2: Frequency of cough scores in Althaea officinalis treatment

| Group | Cough Scores | | | | |
|------------------|--------------|----|----|----|---|
| | 0 | 1 | 2 | 3 | 4 |
| Althaea | | | | | |
| Before treatment | 0 | 4 | 8 | 12 | 6 |
| After treatment | 8 | 11 | 7 | 4 | 0 |
| Placebo | | | | | |
| Before treatment | 0 | 3 | 6 | 18 | 3 |
| After treatment | 1 | 3 | 10 | 15 | 1 |

Values are absolute frequency

Table 3: Change in spirometry data with Althaea officinalis

| Parameter | Althaea Group | | Placebo Group | |
|-----------|------------------|-----------------|------------------|-----------------|
| | Before treatment | After treatment | Before treatment | After treatment |
| FVC | 83.66±12.62 | 82.40±11.08 | 81.26±7.42 | 81.06±6.77 |
| FEV1 | 85.50±13.42 | 85.51±12.32 | 81.6±9.52 | 81.4±10.03 |
| FEV1/FVC | 103.56±11.75 | 102.76±11.29 | 99.5±11.52 | 99.13±9.80 |
| PEF 25-75 | 89.66±22.36 | 85.80±21.99 | 86.13±31.30 | 85.03±25.30 |

Values are mean±SD. P>0.05 between all before and after treatment values and between Althaea and placebo groups.

They were asked to score their cough severity before and after of intervention according to the following scale : 0, no cough, 1, which was only a tickling sensation on the throat, 2, mild cough, which did not interfere with daily activities, B, moderate cough, which was tolerable but severe enough to interrupt daily activities for some time, and 4 sever cough, which persisted and interfered with most of the daily activities or disturbed sleep at night.

After the 4 week treatment period, three of patients were excluded from study because Test of drops lead to discontinue compliance of them.

Analysis: Results are expressed as mean ± SD data between the 2 treatment groups were compared by use of the student t test for normal distribution and continuous variable and Mann-Whitney U test for others. Statistical significance was assumed at P< 0.05.

Results

The mean cough score in the Althaea group was 2.66±0.95 at the before intervention and 1.23±1 at the after treatment. There was a significant reduction with Althaea officinalis (Table 1, P<0.05). No significant change in cough scores was found in placebo group (Table 1). Frequency changes in cough scores of the after treatment periods are shown in the Table 2. Eight

of the 30 subjects in the althaea group showed improvement in cough scores. Whereas only one of the 30 subjects in the placebo group showed improvement. No significant difference was observed in spirogram including FVC, FEV1, FEV1/FVC and PEF 25-75 between the Althaea group and placebo groups (Table 3). Complication associated with Althaea administration were reported.

Discussion

It is evident that the cough is a major limitation in terms of continuing the ACEI medication. The frequency of cough has been reported to be higher in women and non smokers for unexplained reasons (Os *et al.*, 1992; Moore *et al.*, 1993; Lee *et al.*, 1996).

There have been various reports that have tried to explain the mechanism of this side effect (Morice *et al.*, 1987; Gilchrist *et al.*, 1989). Bradykinin and prostaglandins are the most frequently proposed causes of the cough and many studies using nonsteroidal anti inflammatory drugs such as sulindac and indomethacin, have been undertaken to attempt to abolish this side effect and thus allow continued medication (Gilchrist *et al.*, 1989; Fogari *et al.*, 1992; McEwan *et al.*, 1990).

One of the mechanisms believed to be associated with the vasodilator effect of ACEI involves the increased generation of No through various mechanisms, including the induction of NOS, and this is now known to be one of the major mechanisms of vasodilation or reduction of myocardial oxygen consumption due to ACEI use (Linz *et al.*, 1999; Sudhir *et al.*, 1996; Zhang *et al.*, 1997; Cannon, 1998). Besides its vasodilating effect, No is also known to have proinflammatory effects on various kinds of cells. (Moncada and Higgs, 1993; Lowenstein *et al.*, 1994; Clancy and Abramson, 1995; Dugas and Kolb, 1995). Furthermore, No is known to be released in excess in bronchial epithelial cells of asthma patients (Silkoff *et al.*, 2000; Kharitonov *et al.*, 1994) and has been reported to be an important pathogenic effector in pertussis and other respiratory tract diseases caused by inflammation (Flak and Goldman, 1996; Anonymous, 2001; Hiroshi *et al.*, 2001). One study showed supplementation of iron clearly had a beneficial effect in most of the subjects of ACEI cough, and this effect could not be found in the placebo group. In short, supplementation of iron successfully diminishes ACEI-induced cough and this fact supports the hypothesis that ACEI-induced cough may be associated with excessive generation of No in bronchial epithelial cells (Sang *et al.*, 2001).

The whole plant of Althaea officinalis particularly the root, abounds with a mild mucilage, which is emollient to a much greater degree than the common Mallow. The generic name Althaea, is derived from the Greek, although (to cure), from its healing properties the name of the order, malvaceae, is derived from the Greek, malake (soft), from the special qualities of the mallows

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in softening and healing. All Mallows contain abundant mucilage, and the Arab physicians in early times used the plant as a poultice to suppress inflammation. Its soothing demulcent properties make it very effective in treating inflammations and irritations of the mucous membranes such as the alimentary canal, the urinary and the respiratory organs. The root counters excess stomach acid, peptic ulceration and gastritis it is also applied externally to bruises, sprains, aching muscles, insect bites skin inflammations and splinters. As we show in the present study *althaea officinalis* clearly showed a beneficial effect in most of the subjects, that significant difference was seen with placebo group. We commend that design studies and implement to determine the exact mechanism of *Althaea officinalis* to reduce ACEI induced cough.

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