
The Effect of Captopril and Ketotifin on Nasal Mucociliary Clearance in Healthy Volunteers

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ABSTRACT

Nasal mucociliary clearance (NMCC) is one of the most important host defense mechanisms of the airway system, which largely depends on the coordinated ciliary beats that transfers the mucus and particles to the oropharynx. Environmental factors as well as infections, allergy and cancer may affect NMCC, a variety of inflammatory mediators and pharmaceuticals also have different effects on NMCC. It is possible to measure NMCC by the saccharine test as a simple quantitative reliable method, which can be used to measure the effects of different substances on this important function.

The Aim of this double-blind, placebo controlled, randomized balanced study, is to examine the effects of captopril and ketotifin in single oral doses on NMCC in healthy human volunteers. The settings are the laboratories of the pharmacology department at the college of medicine, Al-Mustansiriya University.

Group A (8 subjects) of volunteers were given single oral doses of captopril 12.5mg, while group B (8 subjects) were given single oral doses of ketotifin 1 mg, and group C (7 subjects) were given placebo. The age range for the subjects was between 19 and 20years, six females and seventeen males. Saccharin transient time (STT) in minutes, was measured by the saccharine test before the drug intake (day 1), and three hours after drug intake (day 2) at the same time of the day and under the same conditions. The study showed reduction in the STT after captopril, and increase in the STT after ketotifin, but these changes did not reach statistical significance in comparison with placebo.

This study could be regarded as a base for further future studies, with the use of more frequent doses of captopril and ketotifin to discover their true effects on NMCC, and the relationship of these properties on the side effects of captopril (particularly cough), and the therapeutic effect of ketotifin.

Key words: captopril, ketotifin, nasal mucociliary clearance.

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INTRODUCTION

Mucociliary clearance (MCC) involves cilia and the layers of mucus on the ciliated epithelium and refers to the movement of particles along a desired path for maximum health. In the upper respiratory tract cilia propel the mucous and its trapped bacteria and particles to the nasopharynx, where it drops to the hypopharynx and is swallowed. The stomach acid then disposes of the unwanted invaders. In the lower respiratory tract the cilia that line the trachea and bronchial tree similarly move the mucous blanket up the trachea and into the hypopharynx for swallowing. ⁽¹⁾

Ciliary beat frequency refers to the number of full whip like movements of the cilia per second-normally 16, and involves the coordination of these movements. ⁽²⁾ Fortunately, measurement of nasal cilia is an excellent indicator of tracheobronchial function. Numerous authors have reported a good correlation between the saccharin nasal test of MCC in the nose and various tests of MCC in the tracheobronchial tree.

Verra (1993) reported on ciliary dyskinesia with situs inversus, bronchiectasis, chronic sinusitis and sterility. He found the abnormal nasal cilia samples correlated with the bronchial biopsies.

Thus, by using the easily performed saccharin test to measure MCC in the nose, we have an indicator of what the chest MCC is like and can treat accordingly. ^(3, 4) The saccharin test of MCC was first described by Andersen and colleagues in 1974 and is performed in the same manner today ⁽⁵⁾. Because the test is so easy to do, we can evaluate our treatment in an objective manner independent of the patient's subjective complaints. Various factors may increase or decrease MCC, environmental factors; e.g. industrial toxins, oil fires and formalin vapor adversely affect MCC. In addition, allergy, infections, cancer, certain systemic illnesses, and medications also have unfavorable effects on MCC. ^(6, 7, and 8)

Wanner *et al* (1996) have specified mediators and pharmaceuticals that have either stimulatory or inhibitory effects on MCC and its component functions; angiotensin II, bradykinin, prostaglandins, leukotrienes, endothelins, cyclic AMP, neurokinin A, nicotine, norepinephrine, histamine, vasoactive intestinal peptide and

substance P were among substances that enhance ciliary beat frequency (CBF).

While adenosine, eosinophil major basic protein, neutrophil elastase, ACH and platelet activating factor were included with substances that impair CBF. ⁽⁹⁾

The aim of this study is to try to elucidate the effect of some drugs which are known to act by influencing one or more of the above mentioned on MCC. These drugs include the angiotensin converting enzyme inhibitor captopril, which has been associated with the troublesome side effect of cough, related in previous studies to some of the mediators mentioned by Wanner *et al* ^(10,11), and the antihistaminic drug ketotifen whose pharmacological actions were also related to some of the mediators mentioned in the Wanner *et al* study. ⁽¹²⁾

SUBJECT & METHODS

Normal healthy volunteers were chosen for the study and a detailed medical history was taken. Those who received antibiotics or had a history of upper respiratory tract infection in the two weeks before the study and those with obvious nasal obstruction, or septal deviation were excluded from the

study. The volunteers were randomly assigned to three groups: group A consisting of (8) volunteers (5 males and 3 females) aged from 19-21y were given captopril 12.5mg orally as a single dose, while group B consisted of (8) volunteers (7 males and one female) aged from 19-20y received oral ketotifen 1 mg orally as a single dose, and group C consisted 7 volunteers (5males and 2 females) also aged between 19 and 20 years were given placebo. All treatments were dispensed in identical radio-opaque gelatin capsules by an independent subject. A double blind technique was followed.

Saccharin test was carried out on two occasions for each volunteer one day apart, before the treatment (day 1) and three hours after the treatment (day 2), at the same time of the day and under the same conditions. The saccharin test was done by placing a 0.5mm particle of a commercially available saccharine tablet approximately 1cm behind the anterior border of the inferior turbinate.⁽¹²⁾ The time elapsing until the first experience of a sweet taste at the posterior nasopharynx is recorded as the nasal mucociliary clearance (NMCC) time or the sacchrin transit time (STT) in minutes. The volunteers were asked to sit up during the entire period of testing and instructed not to sniff, eat or drink and to

avoid sneezing and coughing if possible. The data were analyzed statistically using the student's t-test.

RESULTS

The mean STT of our volunteers was reduced after administration of captopril, and prolonged after ketotifin, in comparison with placebo, but these changes did not reach statistical significance (Table 1).

Table (1): Mean +/-SD of STT in healthy volunteers before and after captopril, ketotifin and placebo.

Drug	No. of volunteers	SST before drug	SST after Drug	Difference	
placebo	7	8.92+/-3.19	9.51+/-3.88	0.59+/-2.56	t=0.61 p>0.05
ketotifin	8	9.66+/-4.12	11.23+/-1.98	1.57+/-3.83	t=1.23 p>0.05
captopril	8	9.97+/-2.76	8.59+/-2.54	-1.37+/-2.51	T=1.44 p>0.05

through Ca⁺⁺-dependent prostaglandin E2 release.⁽¹¹⁾

DISCUSSION

A large body of literature has accumulated regarding drug induced changes of mucociliary clearance and its component functions. Both stimulatory and inhibitory effects are of clinical significance; the former in relation to airway therapy, the latter as undesired adverse effects of drugs administered for other indications. ⁽¹²⁾

We examined the effects of single oral doses of captopril and ketotifin on MCC in healthy volunteers as measured by the STT. Captopril reduced the mean STT in our study but this reduction did not reach statistical significance. A previous study has proved that bradykinin which is a vasoactive peptide known to be increased by captopril, interacts with B2-type receptors and stimulates ciliary activity

While another study has pinpointed PG2 as playing a leading role in the genesis of angiotensin converting enzyme inhibitors associated cough.⁽¹⁰⁾

Whether this dry bothersome cough linked to captopril use is related to reduced MCC or not, is a subject that requires further investigation. Ketotifin prolonged the mean STT which was also statistically insignificant; this can be supported by an earlier paper that showed the inhibitory effect of ketotifin on platelet activating factor (PAF)-induced ciliary beat frequency decrease which may contribute to the therapeutic property of this antiallergic drug, ⁽¹²⁾ in addition to the well known

pharmacological effect of ketotifen as an antihistamine [histamine is an enhancer of CBF] ⁽⁹⁾ and a mast cell stabilizer.

It also inhibits chemotaxis and eosinophil activation ^(14, 15, and 16). We acknowledge that the present study is groundwork. Future studies using more frequent doses of the drugs and recruiting larger number of volunteers are recommended to uncover adequate information on the effect of these drugs on MCC.

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