

THE EFFECTS OF ZOLMITRIPTAN ON NASAL MUCOCILIARY CLEARANCE (NMCC): RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Nasal mucociliary clearance (NMCC) is one of the most important host defense mechanism of the respiratory system. Many factors like environmental, infections allergy and cancer may affect NMCC. As well as variety of inflammatory mediators and pharmaceuticals also have different effects on NMCC. It is possible to measure NMCC by the saccharine test as simple quantitative reliable method, which can be used to measure the effects of different substances on this important function. This study was designed to evaluate the effects of single oral dose of zolmitriptan 2.5 mg on NMCC in healthy volunteers; this study was double blind randomized balanced study.

Twenty subject; 10 males and 10 females were enrolled in this study and divided into two groups; group A take placebo and group B take zolmitriptan, then saccharin transient time (STT) measured in minute before & after intake of both of placebo and zolmitriptan. Results showed that placebo produced insignificant effects on STT but zolmitriptan prolong STT significantly. The conclusion of this study is that zolmitriptan decrease the NMCC, so patients with chronic obstructive disease suffering from migraine may be affected by this drug, also zolmitriptan may be beneficial therapeutic remedy for respiratory allergy.

Keyword: Nasal mucociliary clearance, zolmitriptan

INTRODUCTION

Nasal Mucociliary Clearance (NMCC) apparatus consist of cilia and layers of mucus on the ciliated epithelium and refer to the movement of particles along a desired path for maximum health, in upper respiratory tract the cilia propel the mucus and its trapped bacteria and particles to the nasopharynx, where it drops to the hypo pharynx and then it will be swallowed, but in lower respiratory tract the cilia that line the trachea and bronchial tree move the mucus upward for swallowing, therefore, the cilia in upper respiratory tract moved downward while the cilia in lower respiratory tract moved upward¹.

Measuring the speed at which particles are moved by cilia gives us objective information about one of the most important physiological actions of the respiratory tract. Because many drugs enhance but other reduce the mucociliary clearance so we can evaluate various drugs as to this action². The saccharin test was first described by Anderson and colleagues in 1974 and is performed in the same manner today³. This test can evaluate our treatment in an objective manner independent of the patients subjective complaints. Many factors affect (NMCC) like industrial toxin, oil fire and formalin vapor, also diseases like allergy, infections, cancer and medications decrease the NMCC^{4,5,6}. The cilia movement depend on ciliary beat frequency (CBF); which is affected by many mediators these are angiotensin II; bradykinin, prostaglandins, histamine and substance P. Those mediator increase CBF so increase NMCC while ACTH, alpha adrenergic agonist and platelet activating factor decrease CBF so decrease NMCC⁷. Also serotonin play an important role in ciliary function by acting on specific serotonin receptor called 5HT (5-hydroxytryptamine) receptors⁸. Zolmitriptan bind with higher affinity to human recombinant 5HT1D and 5HT1B receptors and exhibits modest affinity for 5HT1A receptor but has no significant affinity or pharmacological activity at 5HT2, 5HT3, 5HT4 and other receptors⁹. Zolmitriptan mainly used for treatment of acute attack of migraine headache by direct vasodilatation or inhibit release of sensory neuropeptide substance P and calcitonin gene related peptide through nerve ending of trigeminal system⁽¹⁰⁾. Moreover, zolmitriptan inhibit release of the proinflammatory mediators¹¹. The peak plasma concentration occurring in 2hr., this drug is then converted to active N-desmethyl metabolites. The mean elimination half-life of zolmitriptan and its active metabolite is 3 hr¹². Because zolmitriptan affect the substance P and other proinflammatory neuromediator in addition to 5HT agonist effect so we try to elucidate its effect on NMCC. Therefore; the aim of this study is to elucidate the effect of zolmitriptan on NMCC and evaluate its action regarding saccharin test.

SUBJECTS AND METHODS

This study and its consent form were approved by the Research Review Committee of Al-Mustansiriya University College of Medicine. Normal healthy volunteer's age range (20-24) was chosen for the study and detailed medical history was taken. Those who are diseased are excluded from the study. Twenty volunteers (ten males and ten females) divided into two groups group A (5 males and 5 females) given zolmitriptan 2.5 mg tablet and group B (5 males and 5 females) given placebo. All treatment were dispensed in identical radio-opaque gelatin capsules by independent subject so a double blind technique was followed. The saccharin test was carried out on two occasion for each volunteer one before taking the capsule and other after two hours.

The saccharin test was done by placing a 0.5mm particle of commercially saccharin tablet approximately 1 cm behind the anterior border of inferior nasal turbinate¹³. The time elapsing until the first experience of a sweet test at the posterior nasopharynx is recorded as saccharin transit time (STT) in minute. 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 analyzed statistically using the paired student's t-test within each group & unpaired student's t-test between both groups. $P < 0.05$ was considered statistically significant.

RESULT

The mean of STT was prolonged after administration of zolmitriptan to significant effects ($P < 0.05$) while placebo produce insignificant effects ($P > 0.05$) (table 1).

Therefore, the zolmitriptan prolong the STT to significant ratio, also in comparison with placebo showed significant changes ($P < 0.05$) (figure 1)

DISCUSSION

The respiratory epithelium is essential for defense of the airway against inhaled pathogen. When bacteria or particle of less than 0.5 μm in size reach the lower respiratory tract, they frequently adhere to surface mucus that is convey it to the nasopharynx and periodically swallowed, the efficacy of this mucociliary clearance depend on the function of healthy ciliary beating frequency¹⁴.

The ciliary beat frequency (CBF), can be increased by direct Ca^{+2} dependent mechanism that generate the rapid increase in CBF associated with oscillation or by an indirect Ca^{+2} dependent

mechanism through ATP generation¹⁵. Also CBF stimulated by β_2 -agonist and prostaglandin due to an up regulation of cGMP, but in our study the CBF not measured directly, but assessed by saccharin test that determine the saccharin transient time STT. Furthermore; the mucociliary clearance and CBF are highly impaired by acute disease, so acute ciliary dysfunction not only impaired by acute respiratory infection but also in patient admitted with a variety of underlying diseases including congestive heart failure and

decompensate diabetes mellitus¹⁶. The result of our study showed that zolmitriptan prolong STT considerably when compared with placebo ($P < 0.05$), this effects may be due to many effects on the nasal mucociliary clearance either on substance P or on proinflammatory mediators, or directly on CBF. On the way to under stance this mechanism ought to review the neuromodulators that regulate the ciliary function.

Table 1: Mean and SD of STT before and after Zolmitriptan 2.5mg tablet

Agents	No. of volunteers	STT before mean \pm SD	STT after mean \pm SD	Difference mean	P value
Placebo	10	8.82 \pm 4.19	7.78 \pm 2.19	1.04 \pm 2	$P > 0.05$
Zolmitriptan	10	9.65 \pm 6.12	16.7 \pm 4.16	7.05 \pm 1.96	$P < 0.05^*$

*significant changes

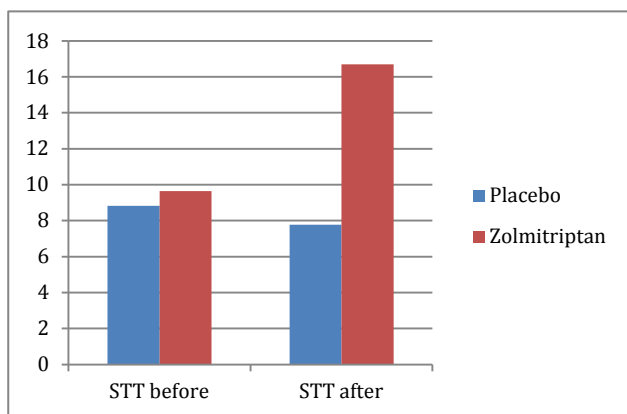


Figure 1: the differences between placebo and zolmitriptan regarding STT before and after each one.

The normal CBF was in the 3-10 Hz range this increased by substance P, prostaglandin and cAMP, consequently terbutalin increase CBF to 12 Hz mediated by stimulation of cAMP and cGMP formation¹⁷. Moreover, histamine, angiotensin II and bradykinin, also improve the CBF for that reason captopril induce coughing by ciliary activation through activation of bradykinin synthesis, nevertheless the inhibitory factors for CBF are platelet activation factor and α -adrenergic stimulation, however; ketotifen prolong the saccharin transient time by inhibition of platelet activation factors¹⁸. It is well known that other factors like ions example Na^+ , K^+ , and Cl^- may be implicated in regulation of CBF, amilorid and frusemid affects the CBF by regulation these ions, as well the increasing in the intracellular Ca^{2+} increase CBF¹⁹. In addition; the mechanism of stimulation of these ciliated cells activate transient receptor potential cation channel subfamily V member 4 (TRPV4) like channel that elevate the intracellular Ca^{2+} the channel opening require the activity of prostaglandin A₂, so TRPV4 regarded as new target to consider in order to develop treatment for pathological with altered mucociliary transport²⁰

Serotonin block the ciliary Cl^- channel lead to increase the influx of Ca^{2+} so improve CBF and then shorten saccharine transient time, but zolmitriptan activate 5HT_{1A} and 5HT_{1B} which are autoreceptor, so when zolmitriptan stimulate these receptor decrease the release of serotonin subsequently less activation on ciliary cell, therefore; Cl^- channel will be open lead to inhibition of CBF²¹. Moreover, serotonin produce direct inhibition on substance P releasing mediated partially by 5HT_{1B}, accordingly zolmitriptan decrease CBF by opening the Cl^- conduit and decrease the excitatory effects of substance P. Rizatriptan and naratriptan are selective agonists for both 5HT_{1D} and 5HT_{1B} produce inhibition of ciliary movement and decrease CBF²². A large body of literature has accumulated regarding drug induced changes of mucociliary consent and its constituent functions, both stimulatory and inhibitory effects are of clinical significance, the earlier in relation to airway therapy, the concluding as undesirable adverse effects of drugs administrated for other indications. This present study showed that zolmitriptan prolong STT, a previous study has proved that serotonin and other

vasoactive peptide known to be augmented by serotonin receptor agonist²². Another study has pinpointed prostaglandin as playing a leading role in the beginning of angiotensin converting inhibitors associated cough²³.

Regarding these cumulative studies, our study presents the zolmitriptan as new therapeutic modality by inhibiting the ciliary function so lessen the allergic response regarding the mucociliary clearance. In this manner zolmitriptan may produce beneficial effects by lessen the respiratory cilia hypersensitivity that are associated with cluster headache and angiotensin converting enzyme inhibitor induced cough.

The conclusion of this study is that zolmitriptan decrease the NMCC, so patient with chronic obstructive disease suffering from migraine may adversely affected by this drug while zolmitriptan may be beneficial therapeutic remedy for respiratory allergy.

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