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

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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 saccharin 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.

Twentysubject; 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 produce 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 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 mucous and its trapped bacteria and particles to we to try to swallow, where it drops to the hypopharynx and then it will swallowed, but in lower respiratory tract the cilia that line the trachea and bronchial tree move the mucous upward for swallowing therefore, the cilia in upper respiratory tract moved downward while the cilia in lower respiratory tract moved upward.

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 action: The saccharin test was first described by Anderson and colleagues in 1974 and is performed in the same manner today. 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. 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 NMCC. Also serotonin play an important role in ciliary function by acting on specific serotonin receptor called 5HT(5-HT) 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 receptors 5HT1A mainly used for treatment of acute attack of migraine headache by direct vasodilatation or inhibit release of sensory neuropeptide substance P and calcitonin gen related peptide through nerve ending of trigeminal system. Moreover, zolmitriptan inhibit release of the proinflammatory mediators. The peak plasma concentration occurring in 2hr, this drug is then converted to active N-desmethyl metabolites. Then removal elimination half-life of zolmitriptan and its active metabolite is 3 hr. 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-Mustansiryah 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 turbinate. 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 pair 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) (figure1)

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 swallowing. The efficacy of this mucociliary clearance depend on the function of healthy ciliary beating frequency . The ciliary beat frequency (CBF), can be increased by direct Ca²⁺ dependent mechanism that generate the rapid increase in CBF associated with oscillation or by an indirect Ca²⁺ dependent
mechanism through ATP generation. Also CBF stimulated by β2-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 mellitus. The result of our study showed that zolmitriptan prolong STT considerably when compared with placebo (P < 0.05), this effect 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 understand this mechanism we ought to review the neuromodulators that regulate the ciliary function.

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

<table>
<thead>
<tr>
<th>Agents</th>
<th>No. of volunteers</th>
<th>STT before mean ± SD</th>
<th>STT after mean ± SD</th>
<th>Difference mean</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10</td>
<td>8.62±4.19</td>
<td>7.76±2.19</td>
<td>1.04±2</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>10</td>
<td>9.65±6.12</td>
<td>16.7±4.16</td>
<td>7.05±1.96</td>
<td>P&lt;0.05*</td>
</tr>
</tbody>
</table>

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 terbutaline increase CBF to 12 Hz mediated by stimulation of cAMP and cGMP formation. 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 factors. It is well known that other factors like ions example Na+, K+; and Cl- may be implicated in regulation of CBF, amilorid and frusenid affects the CBF by regulate these ions, as well the increasing in the intracellular Ca2+ increase CBF. 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 Ca2+ the channel opening require the activity of prostaglandin A2, so TRPV4 regulated as new target to consider in order to develop treatment for pathological with altered mucociliary transport.

Serotonin block the ciliary Cl channel lead to increase the influx of Ca2+ so improve CBF and then shorten saccharine transient time, but zolmitriptan activate SHT1A and SHT1B 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 CBF. Moreover, serotonin produce direct inhibit on substance P releasing mediated partially by SHT1B 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 SHT1A and SHT1B produced inhibition of ciliary movement and decrease CBF. 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 administered 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 agonist. Another study has pinpointed prostaglandin as playing a leading role in the beginning of angiotensin converting inhibitors associated cough.

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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REFERENCES


75


