Diuretics in Human Asthma

ASTMADA DİÜRETİKLER

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The past 15 years have seen a rapid expansion of our knowledge regarding the pathophysiology of asthma (1). Airway inflammation plays a central role in asthma. Thus, the widely accepted prophylactic approach to the treatment of asthma is the use of antiinflammatiory agents. In addition to inhaled steroids, other agents sometimes used in the treatment of asthma include methotrexate, troleandomycin, cyclosporin, gold, magnesium sulfate, inhaled heparin and inhaled furosemide (2-4). The diuretic agent furosemide has recently been shown to protect asthmatic subjects against bronchoconstrictor stimuli when administered by nebulisation (5).

The aim of this paper is to summarize the results obtained using inhaled furosemide against a variety of bronchoconstrictor stimuli in asthmatic patients to examine the possible mechanism of action of the bronchial protective effect of furosemide, and to concider the possible future application of this drug in the therapy of asthma.

Sometimes novel treatments arise from chance observations made with existing drugs. The beneficial effects of an inhaled diuretic, furosemide in asthma challenge studies has raised the prospect that diuretics may have a role in the treatment of asthma in the future (6).

In 1988, Bianco et all presented the first data indicating that inhaled furosemide has a protective effect in exercise-induced bronchoconstriction (7). Furosemide is a loop diuretic. It acts as a diuretic by inhibiting the Na, K, 2Cl cotransporter in the ascending limb of the loop of Henle in the kidney (6).

The complex factors underlying smooth muscle contraction and airway wall thickening in asthma include epithelial damage, vascular leakage, neurogenic reflexes, and recruitment of inflammatory cells with mediator release (8). The physicochemical characteristics of the fluid lining the airways affect bronchial reactivity in asthmatic patients, as indicated by the bronchoconstriction induced in these patients by a variety of stimuli that affect the osmolarity of the bronchial environment. The liquid and ion composition of the bronchial lining fluid is largely regulated by ion transport pathways in the epithelial cells of the airways (9).

The greatest insights into the mechanisms of action of furosemide have been obtained from studies in the kidney. Since the major proposed mode of action of furosemide in this model is on ion transport in renal epithelial cells, it is tempting to speculate that the site of action of furosemide in asthma may be the airway epithelial cell. This hypothesis is intriguing and may provide new insight into the biology of asthma, because, at present, there are few data suggesting that epithelial (ion) transport plays a major role in asthma (10).

Protective Effect of Furosemide

Inhaled furosemide has been shown to have a protective effect against bronchial responses to indirectly acting bronchial provocents such as exercise or isocapnic hyperventilation, inhalation of nebulized distilled water, adenosine 5-monophosphate, inhaled lysine aspirin, sodium meta bisulfit, and inhalled allergens (10). In contrast, furosemide

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does not exhibit, a direct protective effect on the bronchoconstriction induced by histamine, methacholine, or prostoglandin F2a (11). It may be of interest that furosemide exerts its anti-asthma effect only when given by inhalation in relatively high doses (20-40 mg) and is not effective after oral administration in doses that cause diuresis (6). Yates et all examined whether chronic treatment with furosemide could improve airway responsiveness to both a direct or indirect challenge using methacholine and MBS respectively. They have found that furosemide delivered at doses of 10-20 mg from a metered-dose inhaler was active in protecting against MBS-induced bronchoconstriction in patients with mild asthma in a dose-dependent manner to a similar degree as that afforded by 30 to 40 mg of furosemide delivered from a nebulizer. However, furosemide delivered four times daily from the metered-dose inhaler over a period of 1 mo failed to improve bronchial responsiveness to methacholine or MBS in patients with mild asthma (12).

Other loop diuretics (such as bumetanide, torasemide, and piretanide) are also available, and their efficacy in protecting the bronchoconstriction induced by different stimuli has been evaluated in asthmatic patients. Furthermore the more potent diuretics these durgs have less protective effect than furosemide. These drugs are less effective than inhaled furosemide, when given by inhalation. This strongly suggests that the anti-asthma effect of inhaled furosemide is unrelated to its diuretic action in other diuretics, including acetazolamide and amiloride, are either not very effective or are ineffective (6,13). Pye et all have shown that when compared with furosemide equivalent diuretic doses of ethacrynic acid have a similar inhibitory effect on sodium metabisulfite-induced bronchoconstriction in asthma (14).

The mechanism of the protective effect of furosemide in asthma are poorly understood and may be multifactorial. By analogy with sodium cromoglycate and nedocromil sodium another possible mechanism of action of furosemide is an effect on inflammatory cells, including mass cells (6,10). Janssen et all reports that nedocromil, cromolyn sodium, and furosemide antagonize voltage-dependent Ca+2 currents in canine airway smooth muscle, but don't directly after K+ or Cl- currents (3).

Bianco et all suggested that the protection is probably the results of a local effect of inhaled furosemide on the bronchial mucosa. In vitro furosemid inhibits Cl- secretion into the bronchial lumen by blocking an electrically neutral Na+ Cl- co-transport process in the basolaterale membrane of epithelial cells. Thus changes in the osmotic and ionic epithelial environment most probably either damper the responsiveness of sensory epithelial receptors and so inhibit the reflex vagally mediated component of the reaction, or reduce the local release of mediators (7).

Furosemid may reduce the ultrasonically nebulized distilled water (UNDW) induced bronchoconstriction at least in part by interfering with the ion transport across the bronchial epithelium. Because furosemid inhibits Na+-Cl-K+ cotransport system when applied on the basolateral, but not on the apical side. Its effect on ion transport in vivo when inhaled is still questionable. However, this mechanism can not be ruled out since the distribution and concentration of inhaled diuretics is not known. It is possible that may have access to the basolateral Na+ 2Cl- K+ cotransport system since permeability of bronchial mucosa is increased in asthma (13). Shimizu et all shown that the protective action of furosemide against UNDW-induced bronchoconstriction may be independent of its direct inhibitory effect on airway mast cell activation (15).

Another potential mechanism relates to the effect of loop diuretics on carbonic anhydrase since acetozolamid, a carbonic anhydrase inhibitor, attenuates hiperventilation-induced asthma. Both furosemide and bumetenide inhibit carbonic anhydrase in vitro, but this effect may lack clinical relevance because of high concentrations used (10).

However, some studies have showed that furosemide doesn't have protective effect on bronchoconstriction in asthma. Karpel et all showed that inhaled furosemide is an ineffective treatment for asthma exacerbations as it produced only a small improvement in pulmonary function during acute bronchospasm (11). Cerrahoğlu et all reported that there was no significant protective role of furosemide in exercise induced ashtma (5).

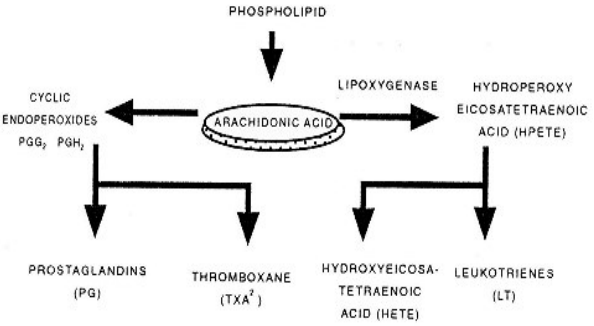

Figure 1. Several eicosanoids play a role in asthma. They are all products of the cyclooxgenase or the lipoxygenase patways of arachidonic acid.

Role of Prostoglandins

Several eicosonoids play a role in ashtma. They are all products of the cyclooxygenase or the lipoxygenase patways of arachidonic acid (Figure 1) (16).

Furosemide increases the production of prostaglandin E2 in the kidney and this action has been related to its diuretic effects. PGE2 is a cyclooxygenase metabolite of human airway epithelium, smooth muscle, alveoler macrophages, and eosinophils (17). It is a potent immunomodulator and a moderate bronchodilator (18). The effects of furosemide are due to generation of cyclooxygenase products in the airway (19).

Although PGE2 under most circumstances acts as a weak contractile agoinst of human airway smooth muscle and has no effect on histamine induced contraction, its effects on histamine induced contraction, its effects on other cells are largely inhibitory. These include inhibiton of mast cell mediator release, neurally induced airway smooth muscle contraction, and inflammatory cell activation. Thus any protective role PGE2 may serve in the airway in vivo would be likely to be against indirectly acting bronchoconstriction challenges rather than directly acting airway smooth muscle spasmogens (17).

Mullol et all reported that the anti asthmatic effect of furosemide may be due to increased synthesis of PGE2 or release in the respiratory mucosa (18). Pavord et all have shown that production of PGE2 may play a role in the inhibitory effect of furosemide (20).

These studies support a role for PGE2 in the protective effects of furosemide and suggest that under certain circumstences edogenously produced PGE2 plays an important bronchoprotective role in the airway (20). Furosemide exerts a prostoglandin-mediated vasodilator effect on renal and pulmonary vascular beds and on systemic veins (10).

Neural Mechanism

Furosemide probably has some effect on airway nerves, but whether this effect plays a role in this protective effect in human asthma is debatable. In vitro, furosemide inhibits both cholinergic and nonadrenergic, noncholinergic contraction of airway smooth muscle. This suggestss furosemide inhibitis the release of tachykinins by C-fibers, an effect which was, in this preparation, independent of the presence of epithelium (10).

Cough and Furosemide

The data confirm previous observations that furosemide reduces cough response to chloride-deficient challenge in normal volunteers (21). Furosemide may modulate their response either directly on the cough receptor or indirectly by changing the local ionic milieu of these receptors (22).

Pietro and et all have shown that inhaled furosemide at the dose used (30 mg) partially inhibits the cough induced by low-chlorid and chloride-free solutions but is ineffective against capsaicin-induced cough. Fine sensory nerve endings situated in the paracellular spaces below the tight junctions of the airway epithelium are generally beliewed to mediate cough reflexes (22).

Inhaled furosemide does not prevent capsaicin-induced cough, which involves release of tachykinins by C-fiber endings, at least in the guinea pig. The protective effective of furosemide against cough induced by nebulized low chloride solutions may be due to modifications of the ionic composition of the microenvironment of the cough receptors rather than to a direct effect, of furosemide on the nerve endings (10).

In summary, there are many putative mechanisms of action of loop diuretics on the airways. The actions of furosemide within the airway are

probably multifactorial. Furosemide inhibits two indirect bronchoconstrictor challenges through a mechanism independent of inhibition of Na, K transport. The possibility that this mechanism involves an interaction with sensory nerves and mast cells requires further investigation (23).

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