Inhaled loop diuretics as potential new anti-asthmatic drugs


Inhaled loop diuretics as potential new anti-asthmatic drugs. S. Bianco, M.G. Pieroni, R.M. Refini, M. Robuschi, A. Vaghi, P. Sestini.

ABSTRACT: The observation that changes in bronchial osmolarity can induce bronchoconstriction in asthma inspired the experimental studies which, unexpectedly, revealed that frusemide is an effective bronchoprotective agent against a variety of osmotic and non osmotic stimuli. Although the mechanism of this protective effect is not fully understood, studies in vivo and in vitro suggest that frusemide may inhibit the activation of different cell types induced by bronchoconstrictor stimuli. Other loop diuretics also exert bronchoprotective activity, but frusemide appears to be the more effective bronchoprotective agent of this family, regardless of their diuretic potency and lipid solubility. Despite the relatively large amount of experimental evidence, there is currently little information on the clinical effectiveness of frusemide in asthma and a long-term controlled study is currently in progress. The observations that treatment with a combination of inhaled acetalsalicylate and frusemide results in a markedly increased bronchoprotective effect compared to either drug alone, opens a new perspective in the possible clinical use of these drugs. Preliminary studies suggest that the association of these drugs is well tolerated and may result in a remarkable steroid sparing effect in patients with steroid dependent asthma, for whom a convenient alternative to long-term steroid therapy is not currently available.

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Introduction

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 [1]. The liquid and ion composition of the bronchial lining fluid is largely regulated by ion transport pathways in the epithelial cells of the airways [2, 3]. The original idea behind the series of acute studies on the effect of frusemide on bronchial reactivity was that, since loop diuretics inhibit the basolateral Na+/K+/Cl- co-transport in epithelial cells [4, 5], this effect could change the bronchial response to osmolar stimuli. Unexpectedly, these experiments demonstrated that inhaled frusemide is a very effective bronchoprotective agent and, hence, a potential anti-asthmatic drug.

The aim of this paper is to summarize the results obtained using inhaled frusemide and other loop diuretics against a variety of bronchoconstricior stimuli in asthmatic patients, to examine the possible mechanism of action of the bronchial protective effect of these drugs, and to consider the possible future application of these drugs in the therapy of asthma.

Effect of inhaled frusemide on experimentally-induced bronchoconstriction

Osmolar stimulants were the first bronchoconstrictor agents against which the effect of inhaled frusemide was tested. In a series of controlled studies we found that inhalation of 40 mg frusemide inhibited the bronchoconstrictor response to ultrasonically nebulized water [6, 7], exercise [8], and hypertonic solutions of NaCl [9]. Under the same experimental conditions, oral frusemide was ineffective, suggesting that the protective effect was due to direct action of inhaled frusemide on the bronchial mucosa. More recently, inhaled frusemide has also been shown to protect asthmatic patients against cold air and hypertonic KCl-induced bronchoconstriction [10, 11], and against blood gas changes induced by ultrasonically nebulized distilled water [12]. The nature of the osmotic changes induced in these models varies considerably, depending on the stimulus: hypotonic aerosols, such as distilled water, are presumed to reduce bronchial osmolarity, whereas hypertonic solutions, exercise and cold air hyperventilation are presumed to have the opposite effect. The fact that significant protection has been observed against all of these stimuli suggests that inhaled frusemide does not counteract the osmotic
changes directly, but probably interferes with mechanisms triggered by these changes, such as stimulation of sensory receptors and/or release of mediators from superficial airway mast cells [13].

The release of preformed and newly generated mediators from superficial bronchial mast cells is very relevant to the bronchial response to allergens [14]. We speculated that if the protective activity of frusemide was, at least partially, mediated by a stabilizing effect on these cells, then frusemide could also inhibit the immediate bronchoconstrictor response to allergens. In controlled studies, inhaled frusemide protected asthmatic subjects from the early and late responses to allergen challenge [15-19], but not from the increase in bronchial reactivity following the late reaction [18]. Inhaled frusemide was also found to reverse the early response, when administered after allergen challenge [18]. The protective effect observed on the late response [19] was also of interest, because the time of its occurrence, 4-8 h after the challenge, frusemide is beyond the estimated duration of action of inhaled frusemide. According to preliminary studies on the distilled water-induced airway response, frusemide is most active in the first hour after administration [20]. In a single study, no further protection against the late response was afforded by a second dose of frusemide administered two hours after challenge (unpublished results). Frusemide presumably exerts its protective activity during the early phase of the reaction, by inhibiting the release of inflammatory mediators necessary for the development of the late response.

In patients with allergic rhinitis, premedication with frusemide has also been shown to prevent the increase in bronchial responsiveness to methacholine that follows the early asthmatic response [17], a finding which we were unable to confirm in a subsequent study in asthmatic patients [21]. Actively sensitized guinea-pigs [16], and dogs [22], were also protected by inhaled frusemide against bronchoconstriction induced by antigen inhalation but not by nonspecific stimuli. An intravenous infusion of frusemide failed to protect guinea-pigs from the anaphylactic response, suggesting that in this model the drug also acts via a local mechanism [16].

Frusemide also gives significant protection against challenge with sodium metabisulphite and adenosine [23-25]. The mechanism of action of these bronchoconstrictor agents is still unknown, but is considered to be, at least partially, mediated by nerve and mast cell activation. In contrast, the bronchoconstrictor activity of methacholine, histamine and prostaglandin F₂α (PGF₂α) is considered to be mostly due to the direct activation of specific receptors on bronchial smooth muscle. In controlled studies, inhaled frusemide did not protect against methacholine in asthmatic patients [10, 23, 26], whereas, a reduction of sensitivity was observed in two studies on normal subjects [27, 28]. Similarly, frusemide caused minimal [29], or no [24, 30], protection against histamine-induced bronchoconstriction, and has had no effect on the bronchial response to PGF₂α [31]. It did, however, cause significant protection against the bronchoconstriction induced by leukotriene D₄ (LTD₄) [30].

The protective activity of frusemide on the respiratory tract is not limited to bronchoconstriction, as it also protects against the tussive response to low chloride solutions [32, 33], and to PGF₂α [31]. In contrast, it was ineffective on cough induced by citric acid [34], capsaicin [32], and metabisulphite [35]. Interestingly, the bronchoconstrictor effect of metabisulphite is inhibited by frusemide [23, 24, 35], but not that of PGF₂α, in contrast to the results obtained on cough induced by the same stimuli.

Possible mechanism of action

A number of other drugs affecting ion transport have been investigated to provide further information on the mechanism of action of frusemide in asthma. Bumetanide and piretanide are loop diuretics of higher potency than frusemide, as far as inhibition of Na⁺/K⁺/Cl⁻ co-transport and on natriuretic activity are concerned [36]. They are also more potent than frusemide in inhibiting ion transport in the dog tracheal epithelium [4], and electrically-induced contraction of guinea-pig bronchial strips in vitro [37]. However, when administered, by inhalation, to asthmatic subjects at doses with equivalent diuretic activity, bumetanide provided significantly lower protection than frusemide against exercise- [38] and adenosine-induced [24] bronchoconstriction, and it had no effect against sodium metabisulphite [24].

Under the same experimental conditions, piretanide showed little protection against distilled water- [39] and metabisulphite-induced bronchoconstriction [40]. Higher doses of piretanide, however, caused significant, dose-related protection against distilled water, and the drug was roughly equivalent to frusemide on an equimolar dose [39]. A newer loop diuretic, torasemide, also had little effect against distilled water-induced bronchoconstriction [41]. The reason for this dissociation between the diuretic and the broncho-protective activities of loop diuretics is not clear. The bronchoprotective activity may be mediated by a mechanism different from the Na⁺/K⁺/Cl⁻ co-transport inhibition, responsible for the diuretic activity. Alternatively, the kinetics of frusemide in the airways might be different from other diuretics, resulting in stronger or longer local activity. The pharmacokinetic properties of frusemide and other loop diuretics after inhalation have not been investigated. Their protective effect, however, does not appear to depend on lipid solubility, as bumetanide and torasemide are highly lipophilic, whereas frusemide and piretanide have low lipid solubility [36].

Increasing information is available on the bronchial effects of drugs active on different ion transport mechanisms. Inhalation of the Na⁺/K⁺/adenosine triphosphatase (ATPase) blocker, ouabain, does not alter the bronchial responses to exercise [1], or histamine
frusemide on exercise-induced bronchoconstriction was ineffective. Flurbiprofen failed to affect the protective activity of frusemide on the response to distilled water and metabisulphite, respectively [58, 59]. The effect of frusemide on bronchoconstriction is mediated by prostaglandins [43, 45]. The carbonic anhydrase inhibitor, acetazolamide, has been shown to reduce the bronchial response to cold air and metabisulphite [45]. Finally, it is interesting to note that sodium cromoglycate, an anti-asthmatic drug with a spectrum of activities very similar to frusemide, has recently been shown to be a potent Cl⁻ channel inhibitor in a mast cell derived tumour line [46].

These findings suggest that ion transport mechanisms participate in the control of bronchial reactivity in asthma, but they do not provide sufficient information to determine the exact mechanism(s) involved. As ion transport pathways are present in virtually every cell type, all cells suspected to be involved in the pathogenesis of bronchial hyperreactivity in asthma are potential targets for the action of frusemide. However, since frusemide has little protective activity on bronchoconstrictor stimuli acting directly on smooth muscle, an effect on these cells appears unlikely. The effects of loop diuretics [4, 5], and allergen challenge [47, 48], on ion transport in the airways have mostly been investigated on the tracheal epithelium of experimental animals. Conflicting results have been reported on the effect of frusemide on human nasal epithelium in vivo [23, 49]. The response of nasal epithelium, however, might not be representative of the action of frusemide at bronchial level, as we failed to observe consistent protection for nasal allergen challenge following frusemide inhalation in patients with allergic rhinitis (unpublished results). Frusemide has been shown to inhibit allergen-induced histamine release from rat peritoneal mast cells [50], and human blood cells [51], and to inhibit the release of histamine and leukotrienes from human lung fragments sensitized in vitro [52]. Other cells, which have been reported to be affected by frusemide, include guinea-pig eosinophils [53], as well as human neutrophils [54, 55], alveolar macrophages [56, 57], and bronchial epithelial cells [57]. No information is available on the effect of loop diuretics on human airway neurotransmission. In the guinea-pig, frusemide and bumetanide inhibit both cholinergic and non-cholinergic neurally-mediated bronchoconstriction in vitro, through a mechanism not influenced by the presence of the epithelium, and which appears to be mediated by inhibition of Na⁺/K⁺/Cl⁻ co-transport [37].

The possibility that the protective activity of frusemide on bronchial reactions is mediated by prostaglandins has been investigated using cyclooxygenase inhibitors. Oral treatment with indomethacin and flurbiprofen failed to affect the protective activity of frusemide on the response to distilled water and metabisulphite, respectively [58, 59]. The effect of frusemide on exercise-induced bronchoconstriction was reversed by oral indomethacin treatment [60]. We have recently observed that inhalation of lysine acetylsalicylate (LASA) strongly potentiates the protective activity of frusemide against distilled water-induced responses [61], and that it has an additive effect against allergen-induced bronchoconstriction [21]. Inhaled sodium salicylate does not potentiate the activity of frusemide, suggesting that the effect of LASA is due to prostaglandin inhibition [62]. Surprisingly, the protective effect of frusemide on exercise-induced reactions also appears to be potentiated by inhaled LASA [63]. Thus, the effect of non-steroidal, anti-inflammatory agents on the protective activity of frusemide appears to depend on the route of administration and possibly on the stimuli and the drugs used.

Therapeutic perspectives

Taken together, these experimental studies indicate that frusemide has a wide spectrum of activity not confined to epithelial cells but extending to other cell types, including neutrophils, eosinophils, macrophages and nerve fibres, all of which are involved in the pathogenesis of asthma. These observations suggest that frusemide might provide a novel approach to the treatment of asthma, or might constitute a starting point for the development of new anti-asthma drugs. Frusemide has not caused bronchodilatation in any of the studies detailed above, or in a controlled study in which specific airway resistance and forced expiratory volume in one second were monitored for 5 h in a group of asthmatic patients with airway obstruction highly reversible after inhalation of fenoterol [64]. In a more recent study, frusemide did not interact with salbutamol-induced bronchodilatation, and the two drugs had an additive protective effect against distilled water-induced bronchoconstriction [65]. A beneficial effect of inhaled frusemide, however, can be expected in patients with bronchial hyperreactivity, due to the prevention of bronchoconstriction. This possibility is speculative at present, and controlled clinical studies to verify the hypothesis are currently being performed. Preliminary results from short-term clinical studies, showing a small beneficial effect of inhaled frusemide in patients with severe asthma [66-69], also need confirmation by ongoing clinical trials. Treatment with inhaled frusemide should, therefore, not be prescribed outside controlled studies until it has been formally validated.

The recent observation that the protective activity of frusemide is greatly potentiated by inhaled LASA and by other prostaglandin inhibitors [60, 62] raises the possibility that the association of the two drugs might provide increased therapeutic activity. Preliminary results from an open study indicate that combined treatment with inhaled frusemide and LASA had a significant steroid-sparing effect in a group of patients with severe, steroid-dependent asthma [70]. Appropriate controlled studies are needed to confirm this observation, and to provide more information on the relative contribution of the two drugs. If confirmed, these results might open new therapeutic perspectives, particularly for patients with severe asthma, for whom
a satisfactory alternative to long-term therapy with systemic steroids is not currently available.

References


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