

Editorial

Inhaled loop diuretics: how do we interpret their modulatory role in asthma?

Classically, diuretics have been in clinical use for several decades to control hypertension and in the management of fluid retention in heart failure and chronic obstructive airway disease. However, over the last 5 years, a number of studies have accumulated evidence in favor of their potential use in bronchial asthma. The “loop” diuretic furosemide, when inhaled, has been shown to protect the asthmatic airways against various bronchoconstrictor stimuli such as allergens (2), ultrasonically nebulized distilled water (UNDW) (28), exercise (6), cold air (14), sodium metabisulfite (19, 21), adenosine 5'-monophosphate (AMP) (21, 25), and bradykinin (27). These interesting findings obviously raise the fundamental question of the mechanism(s) of action of inhaled diuretics in these responses, and many subsequent studies have attempted to shed light on this subject.

“Loop” diuretics act by reducing salt reabsorption in the thick ascending limb of Henle's loop (12) by the inhibition of the Na^+/K^+ -ATPase responsible for the Na-K-Cl cotransport across the tubular epithelium (13, 16). When present at the basolateral side, “loop” diuretics inhibit Cl^- flux by a number of epithelia, possibly by an effect on a linked Na^+/Cl^- entry process (10), supporting the view that the drug may act by blocking Na^+/K^+ -ATPase. However, it is unlikely that the inhibition of the Na^+/K^+ -ATPase at the level of respiratory epithelia may account for their effect in reducing provoked bronchoconstriction. Firstly, experimental evidence indicates that there is no direct inhibition by “loop” diuretics of Na^+/K^+ -ATPase in mammal airway epithelial cells (36). Secondly, these drugs inhibit Cl^- flux only when added to the basolateral side of the epithelium (10), whereas in the challenge studies of asthmatic subjects, “loop” diuretics reached the epithelium from the luminal face of the bronchial mucosa, and they were not effective when given orally (2, 6, 14, 19, 21, 25, 27, 28). Finally, furosemide is appreciably more potent than equidiuretic doses of bumetanide, piretanide, or torasemide in its ability to protect against the bronchoconstriction induced by different stimuli in asthmatic subjects (4, 11, 21, 26), thus suggesting a mechanism that is in-

dependent of the Na-K-Cl cotransporter function. Taken together, these findings argue against the possibility that the mechanism or mechanisms underlying the protective effects of these drugs in experimental models of clinical asthma are the same as that or those responsible for their diuretic properties.

The observation that inhaled furosemide has little or no significant protective effect against methacholine- and histamine-induced bronchoconstriction in asthma (14, 19, 21, 25), suggests that “loop” diuretics have no direct effect at the airway smooth-muscle level. Recent studies on guinea pig tracheal strips (9), bovine bronchial rings, and human bronchial airway smooth muscle *in vitro* (17) prove that neither furosemide nor bumetanide inhibits isometric contractile responses, thus substantiating the view that the protective effect of “loop” diuretics on induced bronchoconstriction *in vivo* is unlikely to be due to a direct effect on airway smooth muscle.

In providing protection against different “indirect” bronchoconstrictor stimuli such as allergens (2), UNDW (28), exercise (6), cold air (14), sodium metabisulfate (19, 21), AMP (21, 25), and bradykinin (27), the inhibitory effect of “loop” diuretics must involve a mechanism or mechanisms common to all these stimuli. Although the inhibitory effects of inhaled furosemide in the airways in the absence of bronchodilation might be explained by a suppressive effect on airway mast cells, with a profile of activity similar to that observed with both sodium cromoglycate and nedocromil sodium, additional possibilities include the capacity of this drug to enhance bronchial blood flow, thus affecting the kinetics of the clearance of bronchoconstrictor stimuli, to inhibit neural pathways, and finally to generate locally protective prostaglandins with functional effects.

Inhaled furosemide seems to exert a preferential protective action against those stimuli, such as allergens (2), UNDW (28), exercise (6), and AMP (21, 25), that cause bronchoconstriction by releasing spasmogenic mediators from various cell types including mast cells. Recently, Temple et al. (33) have shown that furosemide (10^{-6} – 10^{-3} M) can inhibit the IgE-dependent release of histamine and leukotriene C_4 from human lung fragments. Thus, a modu-

latory function of mast cells may be responsible for the protective effect of this and other "loop" diuretics on a variety of mast-cell-dependent bronchoconstrictor stimuli. Furosemide also inhibits the release of superoxide anions from human epithelial cells and alveolar macrophages stimulated by opsonized zymosan *in vitro* (31). However, the substantial protection afforded by furosemide against the airway response to sodium metabisulfite (19, 21) and bradykinin (27), two agonists which are believed to produce bronchoconstriction by sensory nerve stimulation and tachykinin release, suggests that inhibition of mast cells cannot be the sole mechanism of action of furosemide in asthma.

The capacity of inhaled "loop" diuretics to reduce the airway response to exogenously administered bronchoprovocants may also result from a direct effect of these drugs on the bronchial epithelium and underlying vasculature. Through their effect on the Na-K-Cl cotransporter mechanism, "loop" diuretics may increase the chloride and water content of the periciliary fluid (12). In addition, furosemide is an effective vasodilator (1) and, as a consequence, could enhance bronchial blood flow to increase the trans-epithelial clearance of exogenously administered bronchoprovocants. That this also occurs in the allergic airways is supported by a recent study showing that in sheep sensitized to *Ascaris suum* the magnitude and duration of the antigen-induced airway smooth-muscle constriction were influenced by microvascular hyperfusion (8).

There is now some evidence that drugs such as furosemide might alter neural activity in the airways. The recent observation by Ventresca et al. (34) that inhaled furosemide inhibits the cough response induced by low-chloride aerosols in normal volunteers suggests an effect on sensory nerves. Further evidence for an effect on nerves is supported by a recent investigation with guinea pig airways showing that both furosemide and bumetanide inhibit, dose-dependently, the airway smooth-muscle contraction induced by stimulation of cholinergic and noncholinergic nonadrenergic nerves, and that this effect is independent of cyclooxygenase production (9). Furthermore, in asthmatic subjects, inhaled furosemide inhibits bronchospastic responses induced by both sodium metabisulfite (19, 21) and bradykinin (27). Since many of the other "indirect" stimuli also involve, to some extent, neural reflexes, an important component of their bronchoconstrictor response is neurally mediated and probably furosemide-sensitive. However, these findings do not explain the effects of furosemide on the early and late response to allergen (2).

Drugs such as furosemide produce some of their effect in the kidney by the secondary production of endogenous prostanoids (7, 32). In man, furosemide

causes an increase in the plasma concentration of free arachidonic acid (35) and enhances the urinary excretion of prostaglandins (PGs) including prostacyclin (PGI_2) (29). That this also occurs in the airways is supported by a recent report showing that bovine tracheal mucosa produces PGE_2 in response to furosemide (22). It is suggested that furosemide affords protection against exercise and related stimuli by releasing PGE_2 and PGI_2 , which are both potent functional antagonists through their capacity to stimulate adenylate cyclase in the airways (15, 30). In asthma, inhaled PGI_2 affords short-term protection against several stimuli such as exercise (5), UNDW (3), PGD_2 (15), and methacholine (15), without having any consistent effect on basal airway caliber. Similarly, inhaled PGE_2 protects against the contractile effect of sodium metabisulfite and methacholine in asthmatic patients (23). In support of the hypothesis that the effects of furosemide in asthma are due to its ability to generate inhibitory prostanoids, Pavord et al. (24) have recently shown that the protective action of furosemide against exercise-induced asthma is eliminated by cyclooxygenase blockade with indomethacin. Studies with cyclooxygenase inhibitors corroborate a protective role for endogenous inhibitory prostanoids, showing a reduction in the loss of responsiveness commonly observed after recovery from bronchoconstriction induced by exercise (20) and UNDW (18). Thus, it is possible that local production of PGE_2 and/or PGI_2 in response to inhaled "loop" diuretics may account for the protection afforded against the airway effect of exogenously administered bronchoprovocants without changing basal airway caliber.

In this issue of *Allergy*, Bianco et al. (5) challenge the contention that local production of prostanoids modulates the bronchial antireactive activity of furosemide, by investigating the effect of inhaled acetylsalicylate and of furosemide, alone and in combination, on the bronchospastic response induced by UNDW in a controlled study of 15 asthmatic subjects. The results of their investigation show that inhaled furosemide produces a moderate protection of the airways against the constrictor effect of UNDW, whereas nebulized acetylsalicylate produces only a minimal effect. Surprisingly, when they effected interaction of the two drugs, there was a tremendous synergism in terms of the degree of blockade achieved. In the authors' view, their findings suggest that the antireactive activity of furosemide against UNDW is not mediated by the increased production of bronchoprotective prostaglandins. However, it is doubtful that this surmise is substantiated by the data of the present study. Indeed, the unexpected synergistic interreaction between furosemide and acetylsalicylate in the airways of these asthmatic subjects could have completely

masked any contributory role of endogenous prostanooids to the airway effect of inhaled furosemide. Although this bizarre drug interaction gives rise to a novel, interesting observation which may have serious implications for possible future therapeutic options in the management of bronchial asthma, it unfortunately does not broaden our current knowledge of the mechanism(s) of action of "loop" diuretics in human asthma. With these considerations in mind, one is tempted to speculate that local production of inhibitory prostaglandins might be one of the most attractive explanations of the protective actions of "loop" diuretics against the bronchoconstrictor response to various stimuli.

After having been dormant for some years, interest in "loop" diuretics in respiratory medicine has experienced an impressive resurgence, particularly with respect to their potential therapeutic role in asthma as modulating agents of bronchial hyperresponsiveness. Further work is needed to clarify the intriguing suppressive action of this class of drug on bronchoconstrictor stimuli in asthma and whether this has any relevance to a possible therapeutic effect in this disease. However, a better understanding of the range of activity of these compounds in asthma should emerge over the next 5 years as results from long-term clinical trials and isolated airway cell models become available.

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