
LETTER TO THE EDITOR

Effects of frusemide on human airway epithelium

In the June 1990 issue of the Journal, POLOSA et al. [1] show that inhalation of 28±2.5 mg of frusemide reduces the bronchial effects of inhaled methacholine and, to a greater degree, of adenosine 5'-monophosphate (AMP) in asthma. Although increase in the group-average geometric mean of the provocation concentration causing a 20% fall in FEV1 from baseline (PC20) for methacholine is small, and probably due to a large decrease in 4 of 12 subjects (no. 1, 2, 6 and 7), this is an interesting observation that confirms previous findings with 40 mg of inhaled frusemide by FUJIMARA et al. [2].

The authors speculate that the small protective effect against methacholine, and some of the inhibitory effects against AMP are best explained by interference with ion transport by airway epithelium. This is supported by our finding that frusemide deposited on the nasal mucosa causes a dose-dependent decrease in transmucosal nasal potential difference (PD) in man [3], a finding which we have subsequently reproduced (SAILON, REGHARD and LOCKHART, unpublished observation). The reduction in nasal PD strongly suggests either reduced electrical resistance or diminished ionic current across this epithelium; the latter being the most likely because of the known effects of frusemide and other loop diuretics on epithelial cells [4-8]. Therefore, we agree with POLOSA et al. that a direct effect of frusemide on airway epithelium is very likely, and may account for some of the protective effects of this drug against several bronchial provoants [9], the more so since osmotic stimuli, which certainly interfere with ion transport, induce epithelial-dependent relaxation of isolated guinea pig trachea [10].

However, we disagree with POLOSA et al.'s suggestion that frusemide acts via inhibition of the Na⁺-K⁺-ATPase. There is no doubt that Na⁺-K⁺-Cl co-transport of airway, and other, epithelial cells necessitates both establishment and maintenance of a low intracellular Na⁺ activity through operation of the Na⁺-K⁺-ATPase located at the basolateral cell membrane [4-8], and phosphorylation of the co-transporter protein [8, 11]. However, experimental evidence suggests that there is no direct inhibition by loop diuretics of Na⁺-K⁺-ATPase in animal cells [11], including airway epithelial cells [6]. Rather, loop diuretics oppose Na⁺-K⁺-Cl co-transport through a direct effect on the Na⁺-K⁺-Cl co-transporter.

In conclusion, we do agree that frusemide has very likely a direct effect on airway epithelium that may account, at least in part, for its protective effect against bronchial obstruction induced by several bronchial provocants in asthma [3, 9], but we question the primary effect of frusemide on Na⁺-K⁺-ATPase suggested by POLOSA et al. [1]. We also agree with POLOSA et al. that frusemide certainly modifies ion transport and, henceforth, biological activity of other cell types, e.g. mast cells, since Na⁺-K⁺-Cl co-transport is a ubiquitous mechanism [11].

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References
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I read with interest the letter from Wood et al. and was glad to learn that our observations, that frusemide administered by inhalation reduces the bronchial effects of inhaled methacholine in human asthma [1], are in agreement with the findings by Fujiwara et al. [2].

In their letter, Wood et al. propose that frusemide acts via inhibition of Na⁺/K⁺ adenosine triphosphatase (ATPase) at the epithelial level. I agree with them entirely as already mentioned in the discussion of our paper [1], in which we clearly state: "...since the drug inhibits Cl⁻ flux only when added to the basolateral side of the epithelium [3-5] whereas in these experiments the drug reached the epithelium from the luminal face of the bronchial mucosa, it is unlikely that the inhibitory effect of the drug on the epithelial cell Na⁺/K⁺ ATPase may account for its effect in reducing provoked bronchoconstriction".

In contrast to the data presented by Wood et al. [6], a recently published paper has clearly shown that frusemide up to 30 mg has no effect on epithelial ion transport as reflected by nasal potential difference in man [7], thus suggesting that this drug does not affect electrogenic epithelial ion transport. Therefore, whether frusemide has some direct electrogenic effect upon epithelium lining of the respiratory tract remains highly controversial.

Drugs such as frusemide may modulate the bronchoconstrictor responses to inhaled methacholine by a variety of other mechanisms. Frusemide's capacity to generate protective prostaglandins [8] with functional effects [9] could account for some of the inhibition of the bronchospasm provoked by methacholine. Frusemide affects neural function in the inner ear [10] so that it might inhibit both cholinergic and non-cholinergic nervous activity in the airways [11]. Finally, frusemide, in being an effective venodilator agent [12], could also enhance bronchial blood flow and, therefore, affect the kinetics of the clearance of the inhaled mediator.

The capacity of frusemide to produce a greater protection against the bronchospastic response to inhaled adenosine monophosphate (AMP) rather than methacholine [1] suggested the phenomenon of an additional pharmacological action, possibly that of the level of mucosal mast cells. Prompted by the findings in rat mast cells a loop diuretic sensitive cell Ca⁺/Mg⁺ ATPase has been shown to modulate mast cell degranulation to various stimuli [13], we proposed that an additional action on mast cell functions was a likely possibility. However, to date there is no published data in support of the effect of frusemide on human mast cell function and clearly further studies are needed to clarify this hypothesis.

As science advances and new technologies emerge, our hypotheses will require re-examination and modification, but surely up to now the mechanisms whereby inhaled frusemide protect against various bronchoconstrictor stimuli remains uncertain.

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References