Diuretics and asthma

Sometimes novel treatments arise from chance observations made with existing drugs. The beneficial effects of an inhaled diuretic, frusemide (furosemide), in asthma challenge studies has raised the prospect that diuretics may have a role in the treatment of asthma in the future.¹ These observations originate from the observation made by Bianco and colleagues that nebulised frusemide inhibited bronchoconstriction induced by exercise and by nebulised water in asthmatic patients.^{2,3} Since then the inhibitory effect of inhaled frusemide has been shown in a number of "indirect" challenges (which are thought to cause airway narrowing by releasing a bronchoconstrictor rather than via direct contraction of airway smooth muscle). These include bronchoconstriction induced by sodium metabisulphite,⁴ adenosine monophosphate,^{5,6} hyperventilation,⁷ and the early response to inhaled allergen,^{8,9} in addition to exercise^{2,10,11} and fog.^{3,12,13} In this issue of *Thorax* Rodwell and colleagues describe a similar inhibitory effect of inhaled frusemide in hypertonic saline, another indirect challenge (pp 208-14). In contrast to the inhibitory effect on indirect challenges, inhaled frusemide has no protective effect in direct bronchoconstriction induced by histamine, methacholine, or prostaglandin F_{2α}.^{4,5,7,14} These *in vivo* studies are supported by studies showing that frusemide has no effect on contraction of airway smooth muscle *in vitro* even when airway epithelium is intact.^{15,16} This profile of effects is very similar to that observed with sodium cromoglycate and nedocromil sodium, suggesting that these cromones may share a common mechanism of action with frusemide.

Mechanism of action

The mechanism of action of inhaled frusemide in indirect challenge is still not clear but several clues are provided by recent investigations. Frusemide acts as a diuretic by inhibiting the Na⁺/K⁺/2Cl⁻ cotransporter in the ascending limb of the loop of Henle in the kidney.¹⁷ It achieves a high local concentration as it is concentrated within the kidney. It may be of interest that frusemide 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.² This suggests that relatively high local concentrations are required and that the target cell is superficially located within the airway. Bumetanide is a more potent loop diuretic and is a more potent inhibitor of the same cotransporter but it is not effective in the same challenges.^{5,11} Furthermore, the more potent diuretics piretanide and torasemide have less protective effect than frusemide.^{2,13,18} This strongly suggests that the anti-asthma effect of inhaled frusemide is unrelated to its diuretic action. In addition other diuretics, including acetazolamide and amiloride, are either not very effective or are ineffective.^{4,9} Frusemide reduces the epithelial potential difference and short circuit current in airways *in vitro*, suggesting that it may have a direct effect on airway epithelial cells.²⁰ Nebulised frusemide, however, has no effect on nasal potential difference even though amiloride, which blocks sodium transport in the lumen, is effective.⁴

By analogy with sodium cromoglycate and nedocromil sodium, another possible mechanism of action of frusemide is an effect on inflammatory cells, including mast cells. Some of the indirect challenges inhibited by

inhaled frusemide (including the early response to allergen, adenosine, hyperventilation, exercise, and fog) are believed to be mediated, at least in part, by release of mast cell mediators. Indeed, frusemide appears to inhibit the release of histamine and leukotrienes in passively sensitised human lung *in vitro*.²¹ *In vivo* inhaled frusemide inhibits the release of neutrophil chemotactic factor during fog induced bronchoconstriction, suggesting an inhibitory effect on the release of airway mediator in asthma.¹² Furthermore, frusemide has an inhibitory action on mediator release from eosinophils *in vitro*,²² an effect that appears to be due to inhibition of Cl⁻ transport. This may be consistent with the inhibitory effect of frusemide on the late response and on the early airway hyperresponsiveness following allergen challenge.^{8,9}

Although the mechanism of action of cromones in asthma is still uncertain, there is evidence to suggest that they have effects on sensory nerve function; similar findings have been reported with frusemide. Both nedocromil sodium and frusemide modulate neuropeptide release from sensory nerves of guinea pig airways *in vitro*.^{16,23} Frusemide also has a modulatory effect on cholinergic neural responses, which are not affected by mechanical removal of the epithelium and are therefore presumed to be direct neural effects.¹⁶ The protective effect of inhaled frusemide against metabisulphite induced bronchoconstriction in asthmatic patients provides supportive evidence that an effect on sensory nerves may be important. Further evidence is provided by the inhibitory effect of inhaled frusemide on cough induced by low chloride solutions and prostaglandin F_{2α} in normal volunteers.¹⁴⁻²⁶ It is of interest that nedocromil sodium has an inhibitory effect on chloride transport in an isolated vagus nerve preparation,²⁷ suggesting the possibility that frusemide and cromones have a common molecular mechanism of action which involves blockade of a particular type of chloride channel in sensory nerves.

Role of prostaglandins

The fact that frusemide enhances the synthesis of prostaglandin E₂ in the kidney, which may affect renal blood flow,^{28,29} has suggested that inhibitory prostaglandins, perhaps released from airway epithelial cells, may mediate the protective effect of frusemide in some challenges. Support for this is provided by a recent study in which the cyclooxygenase inhibitor indomethacin appeared to reduce the protective effect of frusemide in exercise induced asthma.¹⁰ This is unlikely, however, as inhibitory prostaglandins released by frusemide should also be protective against directly acting bronchoconstrictors such as histamine and methacholine. Furthermore, another cyclooxygenase inhibitor (flurbiprofen) does not modulate the protective effect of frusemide in metabisulphite induced bronchoconstriction.³⁰ Similarly, lysine aspirin potentiates rather than enhances the protective effect of inhaled frusemide in fog induced asthma.³¹ In addition, frusemide has an inhibitory action against certain cough challenges²⁴⁻²⁶ whereas if it released prostaglandin E₂ this would be expected to enhance cough challenge.^{32,33}

Clinical implications

Although inhaled frusemide has a similar effectiveness to

nedocromil sodium in bronchial challenge studies, it is not yet certain whether it has a useful anti-asthma effect in patients with asthma and studies with regular inhaled frusemide are currently under way. The protective effect of frusemide appears to be unrelated to its diuretic action and therefore there is a possibility that compounds that have a more potent anti-asthma effect but are devoid of diuretic activity may be discovered. The molecular mechanism of action of frusemide is still uncertain but it is possible that a particular type of chloride ion channel is blocked and that this channel—presumably in mast cells, other inflammatory cells, and sensory nerves—is also the target for cromones. This may give insight not only into the mode of action of cromones in asthma but also into the mechanisms of allergic inflammation itself, which may lead the way in the future to the development of more potent and longer lasting drugs with a safety margin as enviable as that of cromones. What started out as a curious observation has turned into an area of research well worth pursuing.

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