Effects of New Quinolones on Transepithelial Electrical Potential Difference of Tracheal Mucosa In Vivo

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Superfusion of canine tracheal mucosa with 100 μg each of grepafloxacin and ciprofloxacin per ml reduced the electrical transepithelial potential difference in vivo by more than 50%. This effect was dose dependent, specific for new quinolones, and inhibited by Cl channel blockers, indicating that new quinolones attenuate Cl secretion across the airway epithelium.

The amount and physicochemical properties of airway surface fluid are regulated by electrolyte transport across the airway epithelium (10). Epithelial cells absorb Na from and secrete Cl toward the lumen, and the net ion flux across the cells generates a transepithelial electrical potential difference (PD), which concomitantly promotes water movement across the airway mucosa (15, 16). We and others have previously shown that macrolides inhibit Cl secretion by the airway epithelium in vitro, which may lead to a decrease in sputum volume in patients with chronic respiratory tract infections (6, 14). However, the effects of new quinolones remain unknown and, more importantly, the in vitro findings may not necessarily reflect electrolyte transport in vivo because of the lack of innervation and blood supply. Therefore, we studied the effects of grepafloxacin (GPFX) and ciprofloxacin (CPFX) on the tracheal PD in anesthetized dogs and compared them with those of other classes of antimicrobial agents.

Mongrel dogs were anesthetized, and their tracheas were exposed. The cartilage rings of the upper trachea were then incised axially, and the surface of the membranous portion was fully exposed. An exploring bridge constructed of polyethylene tubing was placed on the surface of the posterior membrane. Contact with the tracheal surface was ensured by continuous perfusion through the bridge with warmed (37°C) and gassed (95% O2–5% CO2) Krebs-Henseleit solution. The perfusion tubing was placed on the surface of the posterior membrane. Several important conclusions emerged from our study, which evaluated the effects of antibiotics on the tracheal PD in vivo. First, GPFX and CPFX decreased the PD by more than 50% and this effect was dose dependent, specific for new quinolones, and inhibited by Cl channel blockers. Thus, new quinolones may attenuate Cl secretion across the airway epithelium.

To elucidate whether the new quinolone-induced changes in the PD were associated with Cl secretion and/or Na absorption by the tracheal epithelium, the Na channel blocker amiloride (10−4 M) (1), the blocker of both the cystic fibrosis transmembrane conductance regulator (CFTR) and the outwardly rectifying Cl channel (ORCC) diphenylamine-2-carboxylate (DPC; 10−4 M) (8), or the ORCC blocker 4,4′-diisothiocyanato-stilbene-2,2′-disulfonic acid (DIDS; 10−5 M) (7) was added to the superfusing solution and, when the responses of the PD reached a plateau, GPFX or CPFX (100 μg/ml) dose dependently decreased the PD, whereas erythromycin, ampicillin, or cefotaxime had no effect (Fig. 2).

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sion, cannot be ruled out. Third, the effects of new quinolones were almost completely inhibited when the airway epithelium was pretreated with DPC, which decreases Cl conductance at the apical membrane through inhibition of both CFTR and ORCC. In addition, we examined the effect of DIDS to determine whether ORCC is involved in the new quinolone’s action and found that the changes in PD were reduced by more than 40% in the presence of DIDS. These results suggest that new quinolones can attenuate airway epithelial Cl secretion by inhibiting both CFTR and ORCC.

To extrapolate these findings to clinical efficacy, there are some issues to be addressed. Airways usually both secrete Cl and absorb Na, but the proportion of each action varies by region and species (15). Since the cumulative area of the distal airways is much larger than that of the proximal airways, biologic properties in small airways may be important. For example, in canines, the bronchial PD is substantially lower than the tracheal PD and Na absorption is predominant in the lower respiratory tract under basal conditions (15). Also, in the human airway epithelium, Cl flux is considered to be symmet-
ric under physiologic conditions (2, 15). However, many inflammatory mediators are known to stimulate Cl secretion across the airway epithelium (3), suggesting that Cl secretion is predominant under pathologic conditions. Thus, we speculate that the inhibitory effects of new quinolones on Cl secretion may be beneficial to patients having increased sputum production. Next, there appears to be a discrepancy between the effective quinolone concentrations used in this study and the concentrations of new quinolones in serum do not accurately reflect local concentrations, since the CFX concentration in airway epithelial lining fluids can be 10- to 15-fold greater than that in serum (5). Likewise, the peak concentrations of CPFX in serum are in the range of 4 to 6 μg/ml (4) and CPFX penetrates bronchial tissues well, producing tissue/plasma drug ratios of between 1.4 and 4.4 (11). Therefore, our in vivo findings might be relevant to the clinical efficacy of these drugs. Further studies in a clinical setting are needed to determine whether the novel antisecretory action of new quinolones represents inhibition of airway hypersecretion.

The mechanism by which new quinolones inhibit airway epithelial Cl secretion remains uncertain. Several airway epithelial functions are controlled by the autonomic nervous system (9), and we have previously shown that the cholinergic neural pathway plays a role in Cl secretion and, hence, maintenance of the epithelial PD in vivo (12) and that CPFX inhibits the release of acetylcholine from the airway cholinergic nerve terminals (13). Therefore, although it is possible that new quinolones have a direct inhibitory action on Cl channels, the inhibition of cholinergic neurotransmission could also be involved.

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