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Title: Synergistic effects between glycopyrronium bromide and indacaterol on a muscarinic agonist-induced contraction in airway smooth muscle

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Body: Rationale: Bronchodilators play an important role in therapy for stable chronic obstructive pulmonary disease (COPD). Anticholinergics and beta₂-adrenoceptor agonists are widely used to improve lung function, symptoms, and QOL of patients with COPD. This study was designed to investigate whether combination of anticholinergics and beta₂-adrenoceptor agonists is beneficial. Combined effects on airway smooth muscle contraction were examined using glycopyrronium bromide (GB), a long-acting muscarinic antagonist (LAMA), and indacaterol, a long-acting beta₂-adrenoceptor agonist (LABA). Methods: For record of isometric tension, the strips of tracheal smooth muscle of guinea pigs were placed in the organ bath and were perfused with the physiological solution at a constant flow rate of 2 ml/min. Results: One nM indacaterol caused a modest (7.9%, n=18) inhibition of 1 μM methacholine (MCh)-induced contraction of tracheal smooth muscle. GB at 3, 10, and 30 nM caused a concentration-dependent inhibition of 1 μM MCh-induced contraction with values of percent inhibition of 11.1, 21.9, and 52.2%, respectively (each n=6). However, when equi-molars of GB were applied in the presence of 1 nM indacaterol, the inhibitory effects of GB (3, 10, and 30 nM) / indacaterol (1 nM) combination were markedly enhanced, with values of percent inhibition of 25.6 (p<0.05), 46.1 (p<0.01), and 91.2% (p<0.01), respectively (each n=6). Conclusions: Indacaterol synergistically potentiated GB-induced relaxation against cholinergic stimulation in airway smooth muscle. These results may underlie the clinical benefit of combination therapy of LABA and LAMA for patients with COPD.