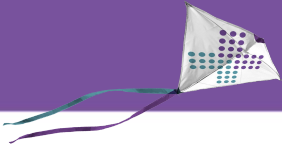




# **[ERS]** Pharmacological characterization of the mechanism of action leading to synergism between glycopyrronium bromide and indacaterol fumarate

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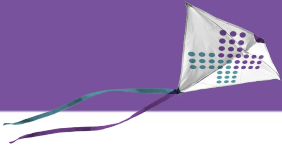


## Introduction.-

Nowadays there is a considerable gap in knowledge concerning the mechanism(s) by which long-acting  $\beta_2$  agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) interact to induce bronchodilation.

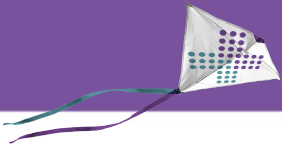
## Objective.-

This study aimed to identify the mechanism(s) causing the synergistic interaction between the LAMA glycopyrronium bromide (GLY) and the LABA indacaterol fumarate (IND) in human bronchial tissue.



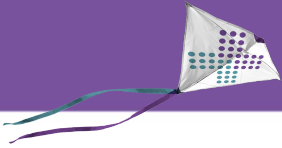
## Methods.-

- The influence of GLY plus IND was assessed on the release of acetylcholine (ACh) and concentrations of cAMP in human isolated airways.
- Iberiotoxin (IbTX, 100 nM) was used to block the  $KCa^{++}$  channels, tetanus toxin (TeTX, 10 nM) to inhibit the synaptic vesicle exocytosis of ACh, and quinine (100  $\mu$ M) to reduce the release of non-neurogenic ACh.



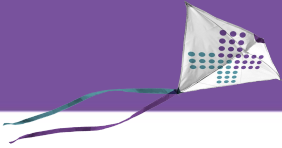
## Results.- (I)

- The co-administration of GLY and IND reduced the release of ACh from epithelial cells ( $-36.6 \pm 4.7\%$ ,  $P < 0.01$  vs. control) but not from bronchi, and enhanced cAMP levels in both bronchi ( $+479.4 \pm 62.4\%$ ,  $P < 0.01$  vs. control) and epithelial cells ( $+29.1 \pm 7.1$ ,  $P < 0.05$  vs. control), an effect that was inhibited by IbTX.



## Results.- (II)

- TeTX inhibited the release of parasympathetic ACh ( $-60.0\% \pm 1.2\%$ ,  $P < 0.001$  vs. control), and both GLY and IND further enhanced this effect ( $-68.4\% \pm 1.8\%$ ,  $P < 0.001$  vs. control).
- Quinine did not influence ( $P > 0.05$ ) the effectiveness of GLY/IND combination in reducing the non-neurogenic release of ACh.



## Conclusions.-

- GLY/IND co-administration leads to a synergistic improvement of bronchodilation by increasing cAMP concentrations in both airway smooth muscle and bronchial epithelium and by decreasing ACh release from the epithelium.