Asthma, respiratory allergy and cough

Effects of selective inhibition of PDE4 by YM976 on airway reactivity and cough in ovalbumin-sensitized guinea pigs

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Question: Phosphodiesterases (PDEs) are enzymes involved in degradation of cAMP and cGMP in many cells. The clinical effectiveness of selective PDE4 inhibitors (e.g. roflumilast) has been confirmed previously in chronic obstructive pulmonary disease associated with neutrophil inflammation. The aim of this study was to evaluate effects of selective PDE4 inhibitor (YM976) on citric acid induced cough, *in vivo* and *in vitro* airway smooth muscle reactivity, and some inflammatory mediators in ovalbumin sensitized guinea pigs with experimentally induced eosinophil inflammation.

Methods: Tested drug was administered intraperitoneally to ovalbumin-sensitized male guinea pigs once daily for 7 days at a dose of 1.0 mg/kg. Double chamber whole body plethysmograph was used for evaluation of citric acid induced cough and for measurement of specific airway resistance after inhalation of histamine. Organ bath method was used for measurement of tracheal and lung tissue strips contractions evoked by cumulative doses of acetylcholine and histamine. Differential counts of blood cells were estimated both in blood and bronchoalveolar lavage (BAL) fluid. ELISA assay was used for evaluation of interleukin (IL)-4, IL-5 and platelet activating factor (PAF) levels in plasma.

Results: Sensitization with ovalbumin led to significant increase in number of coughs, *in vivo* and *in vitro* airway reactivity. Similarly, increased plasmatic levels of IL-4, IL-5 and PAF were observed, with significant increase in differential counts of eosinophils both in blood and BAL fluid. The administration of YM976 suppressed significantly the number of coughs, *in vivo* airway reactivity, and *in vitro* airway reactivity in tracheal tissue strips. Only IL-4 levels were significantly decreased after 7 days administration of YM976.

Conclusions: Our results suggest that PDE4 inhibition by YM976 leads to cough suppression in guinea pigs with ovalbumin induced eosinophil inflammation with suppression of *in vivo* and *in vitro* airway reactivity and positive changes in the markers of inflammation.

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