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Title: Tiotropium combined with budesonide formoterol regulates β_2 receptor in moderate asthma patients: report of 84 cases

作者: 魏艳; 刘芬; 程欣; 刘春涛
四川大学华西医院：临床药物试验中心，呼吸内科； 滕州市中心人民医院呼吸内科

Author(s): Wei Yan; Liu Fen; Cheng Xin; Liu Chuntao
Center of Clinical Drug Trial, Department of Respiratory Diseases, West China Hospital, Sichuan University, Chengdu, Sichuan Province, 610041; Department of Respiratory Diseases, Tengzhou Central Hospital, Tengzhou, Shandong Province, 277500, China

关键词: 支气管哮喘; 布地奈德福莫特罗; 噻托溴铵; 肾上腺素能受体; 胆碱能受体

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摘要: 目的 观察联合应用吸入性糖皮质激素/长效β_2受体激动剂(inhaled corticosteroid/long-acting β_2 agonist，ICS/ LABA)和长效抗胆碱能拮抗剂(long-acting antimuscarinic agent，LAMA)对中度哮喘患者外周血淋巴细胞β_2R的调节作用及意义。 方法 将初治中度持续性哮喘患者分为ICS/LABA组和ICS/LABA+LAMA组，给药前后测定肺功能、ACT评分及AQLQ评分，Western blot检测外周血淋巴细胞β_2受体、M_3受体、PLCβ_1水平。 结果 84例患者给药24周时2组FEV_1值、ACT评分、AQLQ评分均有明显提高，且ICS/LABA+LAMA组较ICS/LABA组改善更为显著(P<0.05)。Western blot检测结果显示，治疗24周后ICS/LABA组外周血淋巴细胞较治疗前β_2AR水平略有下降(P>0.05)； ICS/LABA+LAMA组外周血淋巴细胞β_2AR水平较治疗前变化不大(P>0.05)；ICS/LABA组外周血淋巴细胞M_3R、PLCβ_1蛋白表达水平较治疗前逐渐升高(P<0.05)；ICS/LABA+LAMA组M_3R、PLCβ_1蛋白表达水平较治疗前明显降低(P<0.05)。 结论 β_2受体激动剂的长期使用使哮喘患者出现气道高反应性增高、支气管保护效应下降、急性发作次数增加和病死率上升的现象，可能与M_3R及其通路的活化/表达上调和β_2受体出现脱敏有关，联合LAMA通过拮抗M_3R有可能恢复对β_2受体激动剂的敏感性，从而抵消由于β_2受体脱敏和M_3R及其通路活化引起的不良反应。

Abstract: Objective To investigate the role of the combination of inhaled corticosteroid/long-acting β$_2$ agonist (ICS/LABA) and long-acting anti-cholinergic drugs (LAMA) in regulation of peripheral blood lymphocytes from patients with moderate asthma. Methods A total of 84 moderate persistent asthma outpatients (with asthma over 1 year, 40%≤FEV$_1$%≤60%) in the department of respiratory diseases, West China Hospital during November 2010 to December 2011 were randomly and equally divided into ICS/LABA group and ICS/LABA+LAMA group. Pulmonary function, asthma control test (ACT) score and asthma quality of life questionnaire (AQLQ) score were measured before and after administration. Western blotting was used to analyze β$_2$ receptor, M$_3$ receptor and PLCβ$_1$ in peripheral blood lymphocytes. Results The FEV$_1$ value, ACT score, and AQLQ score of the 84 patients were significantly improved after 24 weeks' administering in both groups. Meanwhile, ICS/LABA/LAMA group improved more significantly (P<0.05 in all). β$_2$AR decreasing trend in ICS/LABA group was not obvious, the protein expression of M$_3$R and PLCβ$_1$ was increased, and in ICS/LABA/LAMA group, β$_2$AR level was unchanged the M$_3$R was significantly decreased, and PLCβ$_1$ was noticeably increased. Conclusion Long-term administration of β$_2$ agonists may lead to the increased airway hyper-responsiveness, reduce bronchial protection effect, increase risks for acute exacerbation, and higher incidence of mortality. This phenomenon may be related to the activation or up-regulation of M$_3$R and its pathway and desensitization of β$_2$ receptors. Combining with LAMA, the sensitivity of β$_2$ agonists might restore the antagonizing M$_3$R, which therefore offset the adverse reactions caused by the desensitization of β$_2$ receptor, as well as activation of M$_3$R and its pathway.

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