الجمعية الصيدلية السعودية
Saudi Pharmaceutical Society

تهنئة

تتقدم الجمعية الصيدلية السعودية بالتهنئة لـ

سعادة الدكتورة/ حنان حمدي حجر

لحصولها على المركز الثاني في المسابقة العلمية لجائزة أفضل ملصق علمي (Poster) ضمن فعاليات المؤتمر السعودي الصيدلي العالمي السابع المنعقد في فندق الفيصلية بالرياض في الفترة من ٢٩ صفر – ٢ ربيع الأول ١٤٢٨هـ الموافق ١٩-٢١ مارس ٢٠٠٧ م

راجين من الله لكم دوام التوفيق والسداد

رئيس مجلس إدارة الجمعية

رئيس اللجنة المنظمة للمؤتمر

١٤٢٨/٤/١١

الدكتور / صالح بن عبدالله السويح

Leukotriene Receptor Blocker, Zafirlukast Attenuates Lipopolysaccharide-Induced Multiple Organ Dysfunction In Rats

Hanan H Hagar

Department of Pharmacology (31), College of Medicine & KKUH, King Saud University, PO Box 2925, Riyadh 11461, Saudi Arabia

Category Pharmacology

Objectives. Lipopolysaccharides are normal components of the cell wall of Gram-negative bacteria and have been recognized for many years as key risk factors in the development of septic shock syndrome. The progression of shock to multiple organ failure is associated with an increase in mortality proportional to the number of organs failing. Despite advances in antimicrobial therapy and critical care medicine, the incidence of septic shock has increased progressively and the mortality rate remains relatively high. Cysteinyl leukotrienes (Cyst LTs) play a pivotal role in the pathophysiology of asthma, psoriasis, ischemia-reperfusion injury and in inflammatory conditions. Although the potent proinflammatory activities of cysteinyl leukotrienes have attracted greater attention in the recent years, but their role in septic shock has not been clarified. Zafirlukast is a potent antagonist of cysteinyl leukotrienes which is used now clinically for treatment of bronchial asthma. The present study investigated the effects of zafirlukast on the organ injury and dysfunction caused by endotoxemia in experimental rats. **Materials.** Sixty rats were used in this study. Animals were classified into four groups of 10 rats each as follow: **Group (I): Control group** animals received saline alone. **Group (II): Zafirlukast group** was treated orally with zafirlukast (20 mg/ kg body weight) for 3 days. **Group (III): Lipopolysaccharide group (LPS)** animals were challenged intraperitoneally with LPS (Escherichia coli 0111:B4, 5.0 mg /kg body weight). **Group (IV, V, and VI): Zafirlukast and LPS groups** were pre-treated orally with different doses of zafirlukast (20, 40 and 80 mg / kg body weight); 3 days later, animals were challenged intraperitoneally with LPS. Animals were killed 6 hour later, blood samples were collected and tissues were harvested. **Results.** Induction of endotoxemia with LPS resulted in increased serum levels of gamma glutamyl transferase (GGT), and aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase

(AST) as a measure of hepatic damage. Animals challenged with LPS also revealed elevated blood urea nitrogen and serum creatinine level (as indicators for renal dysfunction), increased activities of serum creatine kinase and lactate dehydrogenase (heart injury indicators) and serum amylase (a measure of pancreatic injury). Furthermore, LPS injection to saline-pretreated animals resulted in significant increases in serum levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and nitric oxide (NO), suggestive of activation of the proinflammatory response. The involvement of oxidative stress was evident by significant increments in lipid peroxides concentrations measured as malondialdehyde and decrements in reduced glutathione (GSH) levels in heart, liver and kidney of LPS-treated animals. Myeloperoxidase activity suggestive of neutrophil infiltration and activation of the inflammatory response was also elevated in tissues. Zafirlukast pretreatment provided dose-dependent attenuation of the heart, liver and pancreatic injury and renal dysfunction caused by LPS. Zafirlukast reduced the increases in inflammatory cytokines, serum TNF-α, and IL-1β, and serum total nitrite/nitrate level. Prior treatment with zafirlukast reduced myeloperoxidase activities and malondialdehyde levels while increased GSH contents in the heart, liver, and kidney. **Conclusion.** These results indicate that zafirlukast protects against LPS-induced multiple organ damage by inhibiting neutrophil infiltration, balancing oxidant-antioxidant status and suppression of inflammatory mediators. Zafirlukast may serve as a potentially effective prophylactic pharmacological agent in alleviating LPS-induced multiple organ dysfunctions.