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The thalidomide analog 3-phthalimido-3-(3,4-dimethoxyphenyl)-propanoic acid improves the biliary cirrhosis in the rat

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Abstract

Chronic cholestasis and cholangitis may lead to the last phase known as biliary cirrhosis, characterized by cellular necrosis, apoptosis, tissue damage, local regeneration, inflammation and fibrosis. Such events are mediated by cytokines. Thalidomide and its analogs have shown to be effective immunomodulatory and hepatoprotective agents. The aim of this work was to evaluate the hepatoprotective properties of a thalidomide analog, the 3-phthalimido-3-(3,4-dimethoxyphenyl)-propanoic acid (PDA), on bile duct obstruction-induced cirrhosis. Vehicle or PDA (67 mg/kg) was orally administered twice a day to sham (Sham) or bile duct-ligated (BDL) male Wistar rats. The animals were sacrificed 28 days after treatments. Alkaline phosphatase (AP), γ-glutamyl transpeptidase (GGTP) and alanine aminotransferase (ALT) enzyme activities as well as direct and total bilirubins concentration were determined in plasma. Lipid peroxidation (LP), glycogen and collagen were quantified in liver; in addition, histopathology was performed. PDA improved cholestasis, necrosis and fibrosis by significantly diminishing most of liver injury markers ($P<0.05$). Histopathology also showed remarkable liver damage amelioration. PDA effectiveness may be due to its water-solubility, stability, phosphodiesterase-4 inhibitory and immunomodulatory actions. Thalidomide and its analogs seem to be promising drugs for further treatment of biliary cirrhosis.

Keywords: Bile duct ligation; Cholestasis; Cirrhosis; Fibrosis; Liver; Necrosis; Thalidomide; Thalidomide analogs

Introduction

Cholestasis is defined as a disorder of cholepoiesis and bile secretion as well as mechanical or functional stoppage of the bile flow in intrahepatic or extrahepatic bile ducts, with bile components passing into the blood. Persistent cholestasis with concomitant inflammatory and connective tissue reactions as well as all forms of chronic cholangitis may lead to irreversible cholestasis

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