Introduction

The earliest use of ursodeoxycholic acid (UDCA) in the treatment of liver disease dates several centuries back to ancient Chinese folk medicine. However, it was after Iwasaki [1] defined the chemical structure of UDCA in 1936 when the therapeutic properties of this bile acid began to be scientifically evaluated in patients with a wide range of hepatobiliary disorders. In 1975, Makino et al. [2] reported the first prospective study of patients with gallbladder stones treated with UDCA demonstrating gallstone dissolution. In 1985, Leuschner et al. [3] first reported improvement in liver tests of patients with chronic active hepatitis under treatment with UDCA for gallstone dissolution. In 1987, Poupon et al. [4] provided the first evidence of the safety and efficacy of long-term UDCA therapy for patients with primary biliary cirrhosis (PBC). Subsequently, a substantial number of laboratory and clinical studies have defined, to some extent, the mechanisms of action of UDCA and its potential benefits in patients with different hepatobiliary diseases, as reviewed by Trauner and Graziadei in 1999 [5•].

UDCA is a hydrophilic dihydroxy (3α, 7β-dihydroxy-5β-cholan-24-oic acid) bile acid. In humans, UDCA accounts for up to 4% of the bile acid pool. Because UDCA is not synthesized in the liver, it likely originates in the colon by bacterial 7β epimerization of the primary bile acid, chenodeoxycholic. UDCA is then passively absorbed by the colonic mucosa to enter the portal circulation and, subsequently, the pool of bile acids. Oral absorption of UDCA is enhanced by bile acid solubilization, suggesting that it should be taken during meals. However, intestinal uptake of UDCA may be diminished because of intraluminal binding by other concurrent medications such as cholestyramine, cholestipol, activated charcoal, and aluminum-containing antacids. Indeed, it is recommended that UDCA be administered 5 hours apart from these agents. UDCA absorption and bioavailability can be decreased in patients with advanced cholestasis [6].

UDCA has a high first-pass metabolism approaching 70%. This leads to its low blood levels in the systemic circulation. In bile, the UDCA concentration reaches a peak 1 to 3 hours after its oral administration. During continuous UDCA therapy, the UDCA in bile is enriched, accounting for 19% to 64% of biliary bile acids depending on the daily dose, and it becomes the principal bile acid in serum (up to 60% of serum bile acids) and liver (30% of liver bile acids). Nevertheless, UDCA has no notable effect on the total bile acid pool size. In humans, the half-life of UDCA is 3.5 to 5.8 days. The predominant route of elimination from the body is fecal. However, in cholestatic patients, the increased renal clearance of UDCA conjugates represents an important pathway of UDCA elimination [5•,6•].

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UDCA decreases the biliary cholesterol by 40% to 60%; this effect may be accomplished either by decreasing the intestinal absorption of cholesterol or by increasing its conversion to bile acids. In fact, studies have shown that UDCA increases the metabolic conversion of cholesterol to bile acids in healthy individuals, patients with hyperlipidemia, and patients with cholestatic liver diseases [7]. In patients with noncirrhotic stages of primary biliary
Mechanisms of Action
UDCA exerts its actions in the hepatobiliary system through multiple, albeit still incompletely defined, mechanisms (Table 1). Depending on the pathophysiology of the underlying liver disease, the predominant mechanism of action of UDCA may vary. Perhaps the key feature for most, if not all, proposed mechanisms is that the beneficial effects of the hydrophilic bile acid UDCA oppose the toxic effects of other more hydrophobic bile acids. Hence, hepatobiliary disorders characterized by or with a component of retention of toxic bile acids have become the main therapeutic realm of UDCA. The mechanisms of action of UDCA have been extensively reviewed previously [5, 6, 7].

Alteration of the bile acid pool
In patients with cholestasis, the accumulation of bile acids in the liver and peripheral tissue may reach toxic concentrations. This increment of increased bile acids in the liver promotes apoptosis, necrosis, fibrosis, and, ultimately, biliary cirrhosis. Continuous oral therapy with UDCA replaces more hydrophobic (toxic) endogenous bile acids with UDCA, leading to less exposure of the liver and peripheral tissue to the toxic effects of endogenous bile acids. During UDCA therapy, serum levels of primary bile acids, such as cholic and chenodeoxycholic acids, decrease, whereas levels of secondary bile acids, such as deoxycholic acid, are unaffected or may even increase, as happens with lithocholic acid as a result of bacterial conversion of UDCA. The reduction in primary bile acid levels seems to be caused by the inhibition of ileal bile acid absorption by UDCA and the stimulation of hepatocellular bile acid excretion by UDCA.

Cytoprotective effects
Hydrophobic bile acids are potentially hepatotoxic. This toxicity of bile acids is dependent on direct interaction with the target liver cells (hepatocytes) and bile duct epithelial cells (cholangiocytes). Administration of the hydrophobic bile acid lithocholic acid to experimental animals induces liver cirrhosis, and its taurine conjugate, taurodeoxycholic acid, is highly cholestatic. This hepatotoxicity of bile acids may result from their ability to interact with biomembranes, ranging from binding to solubilization of the membranes with the consequent cytolysis or necrosis. Bile acids can also induce apoptosis, the “physiologic” cell death that removes damaged and aged cells from the organism. Hydrophobic bile acid levels seem to be caused by the inhibition of ileal bile acid absorption by UDCA and the stimulation of hepatocellular bile acid excretion by UDCA.

Immunomodulatory activity
During chronic cholestasis, the major histocompatibility complex (MHC) class I and class II molecules are overexpressed in hepatocytes and cholangiocytes. Aberrant expression of MHC class I proteins on hepatocytes may lead to their recognition and subsequent destruction by cytotoxic T lymphocytes. In the bile duct ligated model of cholestasis and in in vitro studies, it has been shown that...