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Urisodeoxycholic Acid in Treatment of Liver Cirrhosis

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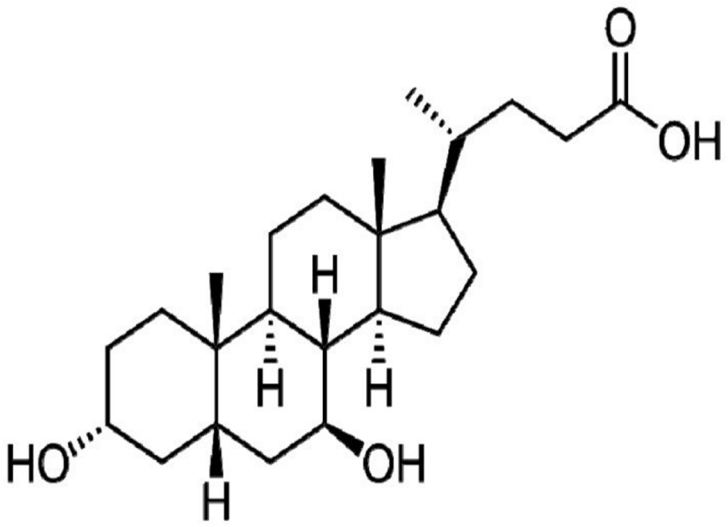
Abstract: ***Ursodeoxycholic acid is a dihy- droxy bile acid with a rapidly expanding spectrum of usage in acute and chronic liver diseases. The various mechanisms of action of this hydrophilic bile acid include direct cytoprotection, detergent action on dysfunctional microtubules, immunomodulation and induction of hypercholer- esis. Its efficacy in primary biliary cirrhosis and primary sclerosing cholangitis as an adjunct to medical therapy has been well established.Ursodeoxycholic acid prolongs survival in primary biliary cirrhosis and it improves biochemical parameters of cholestasis in various other cholestatic disorders including primary sclerosing cholangitis, intrahepatic cholestasis of pregnancy, cystic fibrosis and total parenteral nutrition-induced cholestasis. However, a positive effect on survival remains to be established in these diseases. Ursodeoxycholic acid is of unproven efficacy in non- cholestatic disorders such as acute rejection after liver transplantation, non-alcoholic steatohepatitis, alcoholic liver disease and chronic viral hepatitis. This review outlines the present knowledge of the Pharmacology of ursodeoxycholic acid, and presents data from clinical trials on its use in chronic liver diseases.***
Keywords: Liver cirrhosis, Urisodeoxycholic acid

I. INTRODUCTION

A. History of UDCA

Urisodeoxycholic acid (urisodiol, UDCA) is a hydrophilic dihydroxylated bile acid (chemical structure: 3α, 7βdihydroxy-5β-cholanoic acid) which was first identified in the bile of the Chinese black bear and was named after this species (ursus Lat.=bear). UDCA is also present in very small quantities as a secondary bile acid in humans (1–3% of the total bile acid pool) where it is formed by 7β-epimerization of the primary bile acid chenodeoxycholic acid in the gut by intestinal bacteria. In contrast to humans, UDCA is a primary bile acid in bears and nutria where it is directly synthesized from cholesterol. Dried bear bile has been used for centuries as a remedy for liver disease in China on an empirical basis, based on a long-standing belief that bear bile had curative properties. The structure of UDCA was elucidated in 1936 by Iwasaki and it was subsequently synthesized and marketed in combination with vitamins as a hepatoprotective agent in Japan. Reports from Japan and Europe first revealed that UDCA was able to dissolve gallstones, similarly to chenodeoxycholate, but that it was not hepatotoxic. Leuschner and coworkers were the first to report in the Western literature their observation that UDCA given for gallstone dissolution in patients with chronic active hepatitis also had improved routine liver function tests. Similar observations had previously been made in Japan. These initial reports prompted further studies on the use of UDCA mainly in chronic cholestatic disorders.

B. Structure of UDCA



C. Biochemical Properties of UDCA

Biochemical properties of bile acids . Bile acids are natural steroids synthesized from cholesterol in the liver. After excretion into bile, 95% of bile acids are resorbed in the intestine (mainly in the terminal ileum), returned to the liver, and then re-secreted into bile in an 'enterohepatic circulation'. Bioavailability of UDCA Urisodeoxycholic acid is a 7B epimer of chenodeoxycholic acid. Conversion of chenodeoxycholic acid into urisodeoxycholic acid occurs in two stages via 7-ketolithocholic acid. Urisodeoxycholic acid is a secondary bile acid (produced in the gut) as well as a tertiary bile acid (produced in the liver).About 30-60% of orally administered urisodeoxycholic acid is absorbed. Although poorly water soluble in the protonated form, unconjugated urisodeoxycholic acid is absorbed along the entire length of the jejunum and ileum by non-ionic passive diffusion; about 20% may be absorbed in the colon. The absorption of free urisodeoxycholic acid is facilitated by prior solubilization. The absorption of urisodeoxycholic acid can also be enhanced by administering it as a water-soluble taurine conjugate. Binding agents such as antacids, charcoal and cholestyramine impair the absorption of urisodeoxycholic acid.The high first-pass metabolism (70%) results in low blood levels of urisodeoxycholic acid after an oral dose ll. The half-life of urisodeoxycholic acid is 3.6 to 5.8 days in humans.

D. Pharmacodynamics of UDCA

After oral administration of unconjugated UDCA, 30–60% of the dose is passively absorbed in the small and large intestines, and undergoes efficient hepatic uptake (> 60% of the absorbed dose) and conjugation in the liver with glycine (to a lesser extent with taurine). Because colonic absorption may account for as much as 20% of an ingested dose, unconjugated UDCA is also absorbed in patients who have had ideal resection, as long as high oral doses (4g/day) of UDCA are administered.

E. Pharmacokinetics of UDCA

Urisodeoxycholic acid is absorbed incompletely because of its low aqueous solubility. After absorption, it is conjugated with glycine or taurine and circulates with the endogenous bile acids. At usual doses (8- 10 mg/kg/day), the pool of urisodeoxycholyl conjugates constitutes 30- 60% of circulating bile acids. Urisodeoxycholic acid is metabolized by intestinal bacteriae to lithocholic acid which does not accumulate in the circulating bile acids because of efficient hepatic sulfation.

F. Mechanisms action of UDCA

Urisodeoxycholic acid may act by several mechanisms, all of which are poorly understood . The most obvious one is a relative decrease in the toxic hydrophobic bile acids.This occurs mainly due to dilution of the latter by expansion of the bile acid pool with urisodeoxycholic acid which is hydrophilic, and not because of displacement or reduced formation of hydrophobic bile acids. Analysis of the ultrastructure of bile acids has revealed that, in urisodeoxycholate, the increased distance between – COH groups or placement of a -COH on the beta face of the molecule acts to decrease H-bonding and to increase hydrophilicity for urisodeoxycholic acid compared with chenodeoxycholic acid.

Whether the beneficial effect in liver diseases is because of decreased concentration of endogenous hydrophobic acids or because of the absolute increase in urisodeoxycholic acid levels in circulation is, however, not clear. Certainly, it has been suggested that the hydrophilic nature of urisodeoxycholic acid confers cytoprotection in necro inflammatory diseases of the liver. Although the mechanism by which this is achieved is far from understood, some recent data support its effects, both on the cell membrane and the cellular signal transduction. Elegant studies on isolated hamster hepatocytes and liver cell membrane preparations have shown that urisodeoxycholic acid stabilises the liver cell membrane by binding to certain domains in the membrane structure.

In isolated hamster hepatocytes, urisodeoxycholic acid decreases glucagon-induced cyclic adenosine monophosphate (cAMP) production in a dose-dependent manner. Given the role of cAMP in the regulation of many processes, such as gluconeogenesis, glycogenolysis, bile secretion and synthesis of proteins and DNA, this finding has significant implications. In addition, urisodeoxycholic acid has a mild detergent action on organelle lipids, resulting in preservation of intracellular transport even under conditions of microtubular dysfunction. Finally, urisodeoxycholic acid has been shown to have immunomodulatory action in patients with primary biliary cirrhosis and primary sclerosing cholangitis. It alters the expression of MHC class I and HLA-DR antigens on hepatocyte membranes in these patients. Urisodeoxycholic acid exerts profound hypercholeresis, at least partly because of an efficient cholehepatic shunt. Soon after secretion into biliary ductules, free urisodeoxycholic acid is protonated by an H+ derived from carbonic acid. HC03- released from the breakdown of the latter promotes bile-salt-independent bile secretion while the protonated urisodeoxycholic acid is readily absorbed because of its lipid solubility. Thus, urisodeoxycholic acid returns to the liver via the periductular venous plexus to be secreted again. To what extent this choleretic action of urisodeoxycholic acid helps in cholestatic liver disease, however, remains to be established.

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G. Indications of UDCA

Urisodeoxycholic acid: potential indications

1) Acute Liver Diseases

a) Cholestasis of acute viral hepatitis
b) Acute alcoholic hepatitis
c) Recurrent cholestasis of pregnancy
d) Acute graft-versus-host disease
e) Acute rejection following liver
f) Transplant

2) Chronic Liver Diseases

a) Cholestatic: primary biliary
b) Cirrhosis, primary sclerosing cholangitis * noncholestatic: chronic active
c) Hepatitis, cirrhosis of the liver

II. TREATMENT OF CHOLASTATIC LIVER DISEASES WITH UDCA

A. Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease, occurring mostly in young male patients and frequently associated with inflammatory bowel disease, usually chronic ulcerative colitis. It is characterized by intra- and extrahepatic biliary strictures and bile duct fibrosis associated with inammatory changes involving the portal and periportal regions of the liver. Given the similarities between PSC and PBC, particularly with regard to the profound cholestasis and the deleterious effects of retained toxic bile acids, several trials were initiated to determine the effectiveness of UDCA in the treatment of PSC. Biochemical improvement in serum liver tests was biochemical improvement in serum liver tests was observed in UDCA treated PSC patients in early small and mostly uncontrolled studies.

UDCA did not significantly improve symptoms of PSC after 1-2 years of treatment, but improved histological features in some patients. However, UDCA in combination with endoscopic treatment of dominant structures may substantially improve patient survival, as shown by Stiehl et al. for 65 patients with a mean follow-up of 45 months.

In summary, administration of UDCA in PSC patients at doses of 13-15 mg/kg/day may be justied because a biochemical benifit can be achieved and no alternative treatment is currently available. Prolongation of survival, however, has not yet been demonstrated. In contrast to trials in PBC, the number of PSC patients studied and the median follow-up period have been limited. Moreover, the optimal dose of UDCA remains to be determined. In addition, endoscopic treatment of dominant strictures appears to be an essential adjunct to UDCA therapy.

B. Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder of late pregnancy (third trimester) characterized by pruritus of the mother coinciding with an increase in serum bile acids, aminotransferases and bilirubin. The main consequences are disturbed maternal well-being due to severe pruritus and an increased risk of premature delivery and stillbirth. An initial open label study showed that UDCA improved maternal pruritus and biochemical abnormalities in patients with ICP.

Several subsequent small series and case confirmed these encouraging results. A controlled study of 24 patients demonstrated improvement of pruritus, jaundice and serum liver tests in mothers during UDCA treatment. Most importantly, relevant aspects of fetal outcome were also significantly improved.

All babies of mothers in the UDCA group were delivered at or near term, whereas of seven babies in the placebo group were born before week 36 and one of them was a stillbirth. No adverse effects were observed in mothers or babies. In addition, UDCA decreased elevated endogenous bile acid levels in serum, urine and colostrum of mothers with ICP.

Based on these results, UDCA treatment of ICP may be considered safe for relieving pruritus and improving both biochemical parameters and fetal outcome. However, further larger controlled studies are needed before UDCA treatment of patients with ICP can be generally recommended.

III. TREATMENT OF NON-CHOLASTATIC LIVER DISEASES

A. Liver transplantation-acute Rejection

Initial animal and small open-label human studies suggested that UDCA may be useful in the prevention of acute rejection episodes. Therefore, the possible role of UDCA as an immunomodulatory was further explored in four prospective randomized trials. Three studies, including a total of 134 patients, failed to show a beneficial effect of prophylactic UDCA treatment (at a dose of 15 mg/kg/day) on the incidence of acute rejections following OLT. Only one study, including 52 patients, reported a positive effect of UDCA at a dose of 10-15 mg/kg/day with fewer patients experiencing multiple rejection episodes in the UDCA group, although the number of patients free of rejection did not differ. Nevertheless, UDCA provided a slightly improved survival at 90 days and at 1 year. In summary, these data do not support prophylactic use of UDCA after OLT.

B. Chronic Viral Hepatitis

UDCA alone or in combination with interferon was evaluated in a number of controlled trials for the treatment of chronic hepatitis C. Although some biochemical improvement of serum transaminases was achieved, UDCA failed to improve either the virological response rate or histological features. Thus, UDCA (alone or in combination with interferon) cannot be generally recommended for the treatment of chronic hepatitis C, although a subset of patients with high serum gamma-GT levels (increased to more than threefold)might benefit from UDCA.

C. Non-alcoholic Steatohepatitis

UDCA markedly improved liver function tests as well as the histological grade of steatosis in a small open label series of patients with non-alcoholic steatohepatitis (NASH). The possible benefit of UDCA therapy in patients with NASH should be further investigated in randomized controlled studies before UDCA is generally recommended for treatment of this conditions.

D. Alcoholic Liver Disease

In a placebo-controlled crossover study, administration of UDCA for 4 weeks led to a reduction in serum bilirubin levels, as well as serum aminotransferases, gamma-glutamyl transpeptidase and alkaline phosphatase levels in patients with alcoholic liver cirrhosis who continued to drink .These new perspectives for UDCA in the treatment of patients with alcoholic liver disease deserve further investigation.

IV. CONCLUSION

A. Urisodeoxycholic acid is a hydrophilic bile acid with membrane estabilising, cytoprotective, and imunomodulatory effects on liver cells.

B. The majority of data on the use of urisodeoxycholic acid in cholestasis have been derived from uncontrolled trials.

C. Controlled trials are required before definite recommendations can be made. 4. The efficacy of UDCA is still unproven in the setting of liver transplantation (prevention of acute rejection), NASH, alcoholic liver disease, and drug-induced cholestasis.

D. UDCA cannot be recommended to treat chronic viral hepatitis.

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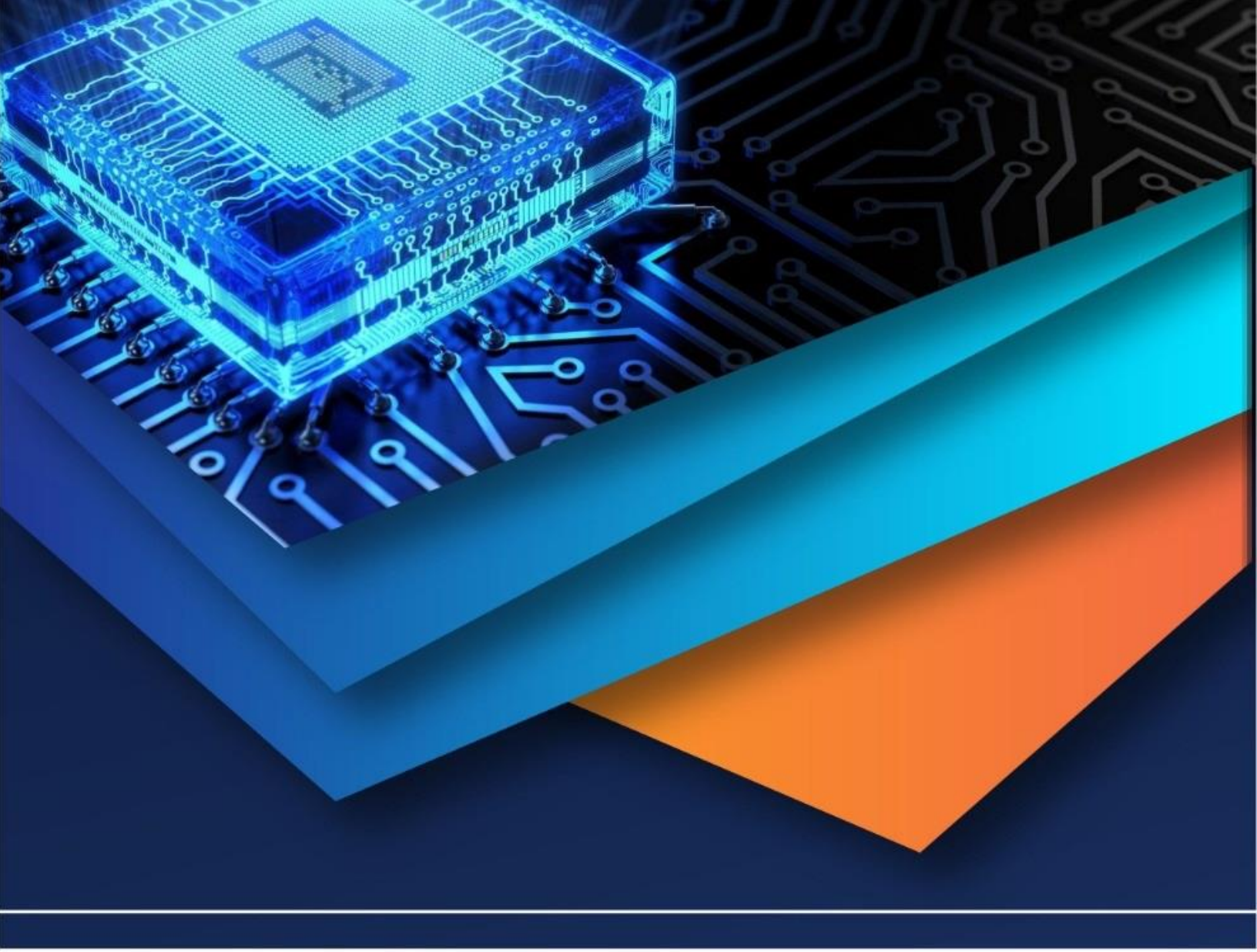

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