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New therapies

Ursodeoxycholic acid in the treatment of liver diseases

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Summary
Ursodeoxycholic acid is a dihydroxy 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 hypercholeresis. Its efficacy in primary biliary cirrhosis and primary sclerosing cholangitis as an adjunct to medical therapy has been well established. Newer indications include its use in the management of chronic hepatitis, cirrhosis, post liver transplant rejection, graft-versus-host disease and acute viral hepatitis, where it not only relieves symptoms of cholestasis but also arrests ongoing hepatocyte necrosis.

Keywords: liver disease, ursodeoxycholic acid

Ursodeoxycholic acid: mechanism of action

- expansion of hydrophilic bile acid pool
- cytoprotection: membrane stabilisation, altered cell signal transduction
- preservation of intracellular transport
- immunomodulatory effect
- hypercholeresis

Box 1

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Therapeutic options for patients with chronic liver diseases are presently far from satisfactory. Ursodeoxycholic acid, a naturally occurring dihydroxy bile acid, is increasingly being considered for the therapy of a variety of chronic liver diseases, especially chronic cholestatic liver diseases. Although the role of ursodeoxycholic acid in liver disease has been appreciated in the Western world only recently, it has been known and utilised in China for centuries. The early preparations were crude – the dried bile of the black bear called 'Yutan' which contains predominantly ursodeoxycholic acid.[1] In Japan, ursodeoxycholic acid has been used since 1957 for a variety of gastrointestinal disorders and, indeed, the first two controlled trials of its use in chronic hepatitis came from there in 1976.[2,3]

The present review focuses on the pharmacology, indications and results of the use of ursodeoxycholic acid in various liver diseases.

Bioavailability of ursodeoxycholic acid

Ursodeoxycholic acid is a 7B epimer of chenodeoxycholic acid.[4] Conversion of chenodeoxycholic acid into ursodeoxycholic acid occurs in two stages via 7-ketolithocholic acid. Ursodeoxycholic acid is a secondary bile acid (produced in the gut) as well as a tertiary bile acid (produced in the liver).[5,6]

About 30–60% of orally administered ursodeoxycholic acid is absorbed.[7] Although poorly water soluble in the protonated form, unconjugated ursodeoxycholic acid is absorbed along the entire length of the jejunum and ileum by non-ionic passive diffusion[8]; about 20% may be absorbed in the colon.[9] The absorption of free ursodeoxycholic acid is facilitated by prior solubilisation by other bile acids. Hence, it is advisable that ursodeoxycholic acid should be taken with a meal that induces gallbladder contraction.[10] The absorption of ursodeoxycholic 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 ursodeoxycholic acid.[7]

The high first-pass metabolism (70%) results in low blood levels of ursodeoxycholic acid after an oral dose.[11] The half-life of ursodeoxycholic acid is 3.6 to 5.8 days in humans.[4]

Mechanism of action

Ursodeoxycholic acid may act by several mechanisms, all of which are poorly understood (box 1). The most obvious one is a relative decrease in the toxic hydrophobic bile acids.[12] This occurs mainly due to dilution of the latter by expansion of the bile acid pool with ursodeoxycholic acid[13] which is hydrophilic, and not because of displacement or reduced formation of hydrophobic bile acids.[14,15] Analysis of the ultrastructure of bile acids has revealed that, in ursodeoxycholate, 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 ursodeoxycholic acid as compared with chenodeoxycholic acid.[16] Whether the beneficial effect in liver diseases is because of decreased concentration of endogenous hydrophobic acids or because of the absolute increase in ursodeoxycholic acid levels in circulation is, however, not clear. Certainly, it has been suggested that the hydrophilic nature of ursodeoxycholic acid confers cytoprotection in necroinflammatory diseases of the liver.[17] 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.[18–23] Elegant studies on isolated hamster hepatocytes and liver cell membrane preparations have shown that ursodeoxycholic acid stabilises the liver cell membrane by binding to certain domains in the membrane structure.[18–20] Furthermore, ursodeoxycholic acid profoundly affects cell signal transduction by mobilisation of intracellular calcium at physiological concentrations.[21,22] In isolated hamster

Ursodeoxycholic acid: potential indications

Acute liver diseases
- cholestasis of acute viral hepatitis
- acute alcoholic hepatitis
- recurrent cholestasis of pregnancy
- acute graft-versus-host disease
- acute rejection following liver transplant

chronic liver diseases
- cholestatic: primary biliary cirrhosis, primary sclerosing cholangitis
- noncholestatic: chronic active hepatitis, cirrhosis of the liver with activity

Box 2

Table 1 Ursodeoxycholic acid in primary biliary cirrhosis (nonrandomised trials). All studies showed beneficial response to therapy

Reference	*No of patients*	*Daily dose*
29	7	600 mg
30	14	10–12 mg/kg
31	10	1800 mg
32	17	7–9 mg/kg
33	10	500 mg
34	29	10–15 mg/kg
35	12	600 mg
36	19	10–15 mg/kg
37	11	10–15 mg/kg

Ursodeoxycholic acid in primary biliary cirrhosis

- clinical impovement
- improvement in liver function tests
- improvement in histology and survival not established
- improvement not seen in advanced disease
- beneficial effect not sustained

Box 3

hepatocytes, ursodeoxycholic acid decreases glucagon-induced cyclic adenosine monophosphate (cAMP) production in a dose-dependent manner.[23] 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, ursodeoxycholic acid has a mild detergent action on organelle lipids, resulting in preservation of intracellular transport even under conditions of microtubular dysfunction.[24] Finally, ursodeoxycholic 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.[25,26]

Ursodeoxycholic acid exerts profound hypercholeresis, at least partly because of an efficient cholehepatic shunt.[27] Soon after secretion into biliary ductules, free ursodeoxycholic acid is protonated by an H^+ derived from carbonic acid. HCO_3^- released from the breakdown of the latter promotes bile-salt-independent bile secretion while the protonated ursodeoxycholic acid is readily absorbed because of its lipid solubility. Thus, ursodeoxycholic acid returns to the liver via the periductular venous plexus to be secreted again. To what extent this choleretic action of ursodeoxycholic acid helps in cholestatic liver disease, however, remains to be established.[28]

Indications for ursodeoxycholic acid

Ursodeoxycholic acid has been tested in various liver diseases (box 2). Primary biliary cirrhosis and primary sclerosing cholangitis are two diseases in which ursodeoxycholic acid has been used most extensively.

PRIMARY BILIARY CIRRHOSIS

This is a progressive cholestatic disease characterised by bile ductular destruction. The interlobular and septal bile duct injury is associated with accumulation of toxic hydrophobic bile salts.[17,25,26] There is also an aberrant expression of HLA class I and class II molecules on hepatocytes and bile duct epithelial cells.[25,26]

There have been several uncontrolled[29–37] (table 1) and randomised controlled[38–47] trials of ursodeoxycholic acid in primary biliary cirrhosis (table 2), most of which have yielded promising results. Because of the small number of patients in each report a meta-analysis would be the preferable method to examine these results. Unfortunately, the methodological variations, differences in inclusion and exclusion criteria, and the different stages at which the patients were included in these studies, preclude a meta-analysis of the existing data. The studies published to date show an improvement in the clinical and laboratory parameters of cholestasis and inflammation (box 3). Significant improvement in the post-treatment values compared with pretreatment values have been reported for serum alkaline phosphatase, alanine transaminase and γ-glutamyl transferase. Improvement in the laboratory parameters occurs within the first few months, reaching a plateau after three to six months of therapy.[31] The effects of ursodeoxycholic acid on laboratory parameters seem to be consistently better than those on clinical manifestations.[39,40,42] A beneficial effect on survival free of transplant (time to transplant or death without transplant) has been reported in a single randomised controlled trial.[49]

Table 2 Ursodeoxycholic acid therapy in primary biliary cirrhosis (controlled trials). No deterioration in symptoms was observed in any study. (Table modified from that of ref 38.)

Reference	*No of patients*	*Duration of therapy (months)*	*Clinical response**	*Biochemical response**	*Histopathological response*
38	20	9	Y	Y	no change
40	88	12	Y	Y	no change
41	45	12	Y	Y	no change
42	145	24	Y	Y	improved
43	222	24	N	Y	no change**
44	180	48	N	Y	no change
45	64	24	N	Y	no change**
46	12	3	Y	Y	no change
47	45	6	N	Y	no change

*Y = significantly improved; N = not improved; **A trend towards improvement was observed even though no objective improvement was documented.

Heathcote *et al* have combined raw data from three large, randomised controlled trials (French, American and Canadian) and followed up these patients subsequently. It has been shown that not only was survival free of transplantation extended with ursodeoxycholic acid (mean of 3.66 *vs* 3.45 years, p=0.014) but the risk of dying or being transplanted was reduced by 32% (11%) in the ursodeoxycholate group.[48] It has also been shown that ursodeoxycholic acid improved survival over that expected from a validated, adjusted model natural history.[49] A trend towards histological improvement has been reported in three controlled trials.[39,42,45] Portal inflammation and piecemeal necrosis have reportedly decreased. In an uncontrolled trial,[30] improvement has also been observed in established fibrosis.

The results of therapy with ursodeoxycholic acid showed a lower efficacy in patients with advanced stages of disease. The improvement in clinical and laboratory parameters is not sustained in these patients, and deterioration has been observed within three or four weeks of discontinuation of therapy, as well as after a year of uninterrupted therapy.[31,50,51] Finally, data have been presented showing histological deterioration accompanied by improvement of clinical and biochemical parameters on ursodeoxycholic acid therapy.[51] Thus, it seems that ursodeoxycholic acid may be useful as an adjuvant for primary biliary cirrhosis rather than as a primary treatment.

PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis is a chronic cholestatic liver disease with inflammation, fibrosis and destruction of the large intra- and extra-hepatic bile ducts.[52] The bile acid profile in patients with primary sclerosing cholangitis has been shown to be similar to that of patients with primary sclerosing cholangitis with increased levels of hydrophobic bile acids.[53] Three uncontrolled[53-55] and placebo-controlled[56,57] trials of treatment with ursodeoxycholic acid in primary sclerosing cholangitis have been reported. An inconsistent improvement in symptoms has been accompanied by consistent improvement in laboratory parameters of cholestasis and necro-inflammatory activity.[53,54] Withdrawal of ursodeoxycholic acid results in deterioration within four weeks.[54] Improvement in parenchymal and portal inflammation and hepatocyte necrosis was observed in a small number of patients.[56] The effect of ursodeoxycholic acid on survival has not been assessed because of the small number of patients. In primary sclerosing cholangitis the role of ursodeoxycholic acid is at best adjunctive to therapy with other agents.

ACUTE VIRAL HEPATITIS

The majority of patients with acute viral hepatitis have a self-limiting illness with a complete resolution and no long-term sequelae. A subgroup of patients with acute viral hepatitis develop a prolonged cholestatic course with intolerable pruritus. Such patients may benefit from ursodeoxycholic acid therapy.

A prospective, randomised, double-blind trial has recently demonstrated that ursodeoxycholic acid may prevent the development of chronic hepatitis B by enhanced clearance of hepatitis B virus.[58]

CHRONIC LIVER DISEASE

The first report of the role of ursodeoxycholic acid in hepatic diseases arose from the serendipitous observation of improvement in levels of transaminases in patients with gallstone disease and coexistent chronic hepatitis.[59] Several randomised double-blind trials of patients with chronic hepatitis have subsequently shown improvement in biochemical parameters (table 3).[60-64] In three of these studies, the duration of treatment was short and, following discontinuation, enzyme values returned to pretreatment levels within four weeks in the majority of patients. The mechanism of action of ursodeoxycholic

Table 3 Ursodeoxycholic acid in chronic liver disease. All studies except ref 60 were randomised controlled studies. All showed a benefit of therapy.

Reference	*Disease*	*No of patients*	*Daily dose (mg)*	*Duration of therapy*
60	chronic active hepatitis	14	10	1 year
	chronic persistent hepatitis	7		
	cirrhosis	82		
61	chronic active hepatitis	36	300	6 months
62	increased transaminases	30	600	
63	chronic active hepatitis	26	450	12 weeks
64	cirrhosis	27	450	6 months

acid in chronic hepatitis may be related to its membrane stabilising, choleretic or immunomodulatory action. The major limitation of this therapy is the lack of antiviral effect. A recent study from Germany has shown that ursodeoxycholic acid has no positive impact on HCV RNA titres or HCV IgM in patients with chronic hepatitis C and the major mechanism for improvement in liver enzymes is the choleretic effect of ursodeoxycholic acid.[65] An Italian study has shown that ursodeoxycholic acid might induce alanine transaminase normalisation in patients with chronic hepatitis C not responding to interferon treatment.[66] In autoimmune hepatitis type 1 ursodeoxycholic acid has been shown to induce a significant fall in IgG and γ-globulins and an improvement in intrahepatic inflammation but not fibrosis.[67]

In combination with vitamin K_1, ursodeoxycholic acid has been shown to reduce the haemorrhagic tendency in patients with decompensated cirrhosis of the liver.[68] On the basis of the existing data, however, no definite recommendation can be made for the dose, duration or efficacy of ursodeoxycholic acid in chronic hepatitis or liver cirrhosis.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Ursodeoxycholic acid has been tried in an open-label trial in eight patients with cholestasis of pregnancy.[69] Significant improvement was reported in pruritus and serum alanine transaminase levels, No adverse effects were reported in the mother or child. All patients had received ursodeoxycholic acid in the second half of the pregnancy, ie, after organogenesis. Randomised double-blind trials are required before ursodeoxycholic acid can be considered as a therapeutic option for intrahepatic cholestasis of pregnancy. Amniotic fluid and umbilical cord bile acid content in patients with intrahepatic cholestasis of pregnancy may pose a threat to foetal well being. Ursodeoxycholic acid may also help in normalising the bile acid profile in umbilical cord blood and in amniotic fluid, thus protecting the foetus from the adverse effects of abnormal amounts of bile acids.[70]

GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease occurs when an immunocompetent donor T cell recognises the recipient's antigens as foreign, resulting in an immune-mediated injury.[71,72] Chronic cholestasis results in up to 80% of patients.[73] The similarity between chronic graft-versus-host disease and primary biliary cirrhosis led to an uncontrolled trial of ursodeoxycholic acid in which 13 patients with chronic refractory graft-versus-host disease were treated with 10–15 mg/kg of ursodeoxycholic acid daily for six weeks. There was symptomatic improvement and biochemical parameters of cholestasis also showed improvement during therapy, although enzyme values returned to pretreatment levels following its discontinuation.[73]

ACUTE REJECTION OF LIVER TRANSPLANT

Acute rejection of liver transplant has been treated with cyclosporine, corticosteroids, antilymphocyte globulin and FK-506.[74] Adjuvant therapy with ursodeoxycholic acid after orthotopic liver transplant may be beneficial (table 4).[75] Patients treated prospectively with ursodeoxycholic acid had fewer episodes of acute rejection than historical controls.[76,77] Ursodeoxycholic acid appears to have a role in preventing recurrent and/or steroid-resistant rejection following orthotopic liver transplant, but the mechanism of action is not known.[78]

Conclusions

Ursodeoxycholic acid is a hydrophilic bile acid with membrane-stabilising, cytoprotective, and imunomodulatory effects on liver cells. It has been shown to

Table 4 Effect of addition of ursodeoxycholic acid to the immunosuppressive regime following orthotopic liver transplantation. From reference 75 with permission from Scandinavian University Press.

Parameter assessed one month after transplantation	*Control (n=8)*	*Ursodeoxycholic acid (n=41)*
Recipients with acute rejection	75%	17%*
Aspartate transaminase (IU/l)	78.1±18.0	42±6*
Alanine transaminase (IU/l)	114.1±24.0	54±12*
Alkaline phosphatase (IU/l)	762±180	366±42**
Bilirubin (μmol/l)	86±34	40±9

*p<0.05; **p<0.01.

exert beneficial effects in various liver diseases, especially those with cholestatic features. The majority of data on the use of ursodeoxycholic acid in cholestasis have been derived from uncontrolled trials. It is reported to have a beneficial effect in primary biliary cirrhosis, primary sclerosing cholangitis and chronic graft-versus-host disease. Potential uses of ursodeoxycholic acid that exploit its cytoprotective properties include fulminant and subacute hepatic failure. Controlled trials are required before definite recommendations can be made.

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