New Therapeutical Indications of Ursodeoxycholic Acid

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Abstract

Until the 1980s the role of bile acids in the initiation of liver injury in man was only suspected on the basis of the toxicity of whole bile and bile salts, and of studies showing elevations in serum and tissue levels of bile salts in liver diseases. The beneficial effects of ursodeoxycholic acid (UDCA) in primary biliary cirrhosis have provided the first firm evidence that bile acids may in some way be related to injury in man.

There are many questions regarding the hepato-protective effect of UDCA that should be addressed in the near future. In particular, we do not know how chronic cholestasis induces liver fibrosis and if UDCA can prevent or counteract this process. Most cholestatic diseases have an immune pathophysiological basis. We must learn much more about the impact of cholestasis and bile acids on the immune system, particularly on endogenous or exogenous peptide presentation in cells exposed to high concentrations of bile components. We have seen that the trafficking of transporters in hepatocytes may be affected by bile acids; efforts must be made to learn more about this important issue. Finally, structural analogues of UDCA or combinations of drugs should be studied, in order to determine if better therapeutic efficacy could be obtained.

Key words

Ursodeoxycholic acid - therapy - cholestasis

Rezumat

Până în anii ’80 rolul acizilor biliari în iniţierea injuriei hepatice la om era doar suspectat pe baza toxicităţii bilei şi a sărurilor biliare, precum şi pe baza studiilor care au evidenţiat creşterea nivelurilor serice şi tisulare ale sărurilor biliare în bolile hepatice. Efectele benefice ale UDCA în ciroza biliară primitivă au reprezentat prima dovadă a posibilei legături dintre sărurile biliare şi injuria hepatică la om.

Există încă numeroase semne de întrebare privind efectul hepatoprotector al UDCA care trebuie lămurite în viitorul apropiat. Nu cunoaştem, de exemplu, modul în care colestaza cronică induce fibroza hepatică sau dacă UDCA poate preveni sau contracara acest proces. Majoritatea bolilor colestatice au o bază fiziopatologică imună. În aceste condiţii trebuie aprofundate cunoştinţele despre impactul colestazei şi al acizilor biliari asupra sistemului imun, în special asupra prezentării de peptide endo- sau exogene în celulele expuse unor concentraţii crescute ale componenţilor biliari. Este cunoscut faptul că circulaţia transportorilor în hepatocite ar putea fi afectată de acizii biliari; trebuie însă intensificate eforturile pentru a cunoaşte mai bine acest fenomen important. Nu în ultimul rând, este necesară studierea analogilor structurali ai UDCA şi a asocierilor medicamentoase pentru a evalua dacă este posibilă obţinerea unor rezultate terapeutice superioare.

Romanian Journal of Gastroenterology
September 2005 Vol.14 No.3, 259-266
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Introduction

UDCA (3α,7β dihydroxy-5β-cholanic acid) (Ursofalk®) is a tertiary bile acid which is more and more frequently used in the treatment of different cholestatic diseases (1,2). It is normally present in human bile, but in a low concentration of only 3% of total bile acids. UDCA is the major component of bile acids in black bear bile, which was used in traditional Chinese medicine for the treatment of liver diseases (3). The first reports on the effect of UDCA in patients with liver diseases appeared in Japan in 1961 (3). Several controlled trials using UDCA in primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) have been published in the literature since 1989 (4). It is worth noting that UDCA has been largely used in the treatment of PBC because it is the only drug approved by the U.S. Food and Drug Administration (FDA).

Pharmacokinetics

UDCA capsules and tablets contain acid cristals with a low solubility at pH < 7. P_{Ka} of UDCA is 5.1, while solubility of the ionic form is 9 mmol/l. After administration of the pharmacological dose (10-15 mg/kg/day), UDCA is absorbed through passive non-ionic diffusion, limited by dilution, mostly in the small intestine and in a small region of the colon (5).

While the critical pH for UDCA micellization is almost pH = 8, UDCA dissolution in the proximal jejunum takes place through solubilization in small micelles with other bile acids (5). Thus, administration of UDCA during meals may increase its absorption. UDCA absorption may be decreased in patients with cholestasis and a low biliary secretion of endogenous bile acids. UDCA is taken up from the portal blood during its first hepatic passage in a proportion of 50% (5), conjugated especially with glycine and less with taurine and actively secreted into the bile. Although conjugates with UDCA appear to be active forms, conjugation even in the cholestatic liver is so efficient that it is apparently sufficient to administer unconjugated molecules. The degree of bile saturation with UDCA correlates with the daily administered dose. A daily dose of UDCA of 13 to 15 mg/kg enriches the bile with bile acids by 40 to 50% in patients with PBC. Over a certain dose, which has not been adequately established, no additional enrichment takes place due to the inability of UDCA to inhibit synthesis of bile acids as well as to the epimerization of UDCA in chenodeoxycholic acid (5). Conjugated UDCA is absorbed mainly in the distal ileon, where it enters into competition with endogenous bile acids for active transportation and undergoes an enterohepatic circulation. Unabsorbed conjugated UDCA reaches the colon, is deconjugated and converted to lithocolic acid by intestinal bacteria.

Due to the fact that its water solubility is low, most of the lithocolic acid remains insoluble in the colon. A fraction of the lithocolic acid reaches the liver again, is sulphated and then excreted into the stool. Even in patients with cholestatic liver disease, less than 5% of the dose of UDCA appears in its conjugated form and metabolites in the urine, showing that only a small part of UDCA is eliminated through the kidneys (5).

Mechanisms of action of UDCA

Experimental evidence suggests three major mechanisms of action:

a. protection of cholangiocytes against cytotoxicity of hydrophobic bile acids;

b. stimulation of hepatobiliary secretion;

c. protection of hepatocytes against bile acid-induced apoptosis.

a. Protection of cholangiocytes against cytotoxicity of bile acids

The liver is responsible for the absorption and transportation of bile acids from the two types of epithelial cells, the hepatocyte and the cholangiocyte. The hepatocyte must also synthetise these products from cholesterol in healthy individuals. Bile acids are essential for lipid emulsion in the intestinal lumen; their synthesis and transport determine bile formation and represent a way of degradation of cholesterol. However, bile acids are also toxic substances. Bile acids bind to proteins and are inserted between the double lipid layers. These effects would have a profound influence on cellular structures and functions if the liver would not efficiently maintain a minimal intracellular concentration. Unfortunately, in cholestasis the excretory pathway from the hepatocytes is blocked, so that bile acids are retained in the liver determining cellular destruction which leads to liver injury. The best example is in children with type II progressive familial intrahepatic cholestasis. These children present a mutation in the bile salt excretory pump, resulting in a failure of the excretion of bile acids as a primary defect ; this is enough to cause liver injury, fibrosis, cirrhosis and death. The mechanisms and prevention of bile acid cytotoxicity present an evident clinical interest.

Because the concentration of bile acids in the bile allows for the appearance of mixed micelles which function as lipid emulsifiers in the intestinal lumen, bile acids are thought to determine cytotoxicity through a “detergent” effect on the cellular membranes.

Phospholipids in bile, by formation of mixed micelles with bile acids, protect cholangiocytes membrane against hydrophobic bile acids. The *mdr-2*-knockout mouse that lacks the ability to secrete phospholipids into bile develops a chronic, nonsuppurative cholangitis resembling human chronic cholestatic liver disease (6).

Enrichment of bile with UDCA renders bile more hydrophilic and less cytotoxic. Feeding of UDCA decreases the degree of cholangiocellular injury, portal inflammation and ductular proliferation in these animals. Likewise, in patients with PBC and PSC under treatment with UDCA, the inflammatory reaction around bile ducts was reported to be less severe (7). The effects of UDCA on cholangiocytes were apparently mediated by Ca^{2+} and protein kinase C-α (PKCα)-dependent mechanisms (8).

Accumulation of bile acids in chronic cholestasis triggers cholangiocyte proliferation. Bile acid stimulation of cholangiocyte proliferation and secretion requires bile acid entry into cholangiocytes through the Na^{+}-dependent apical bile acid transporter (ABAT).

In a recent study, Alpini et al (9) showed that in purified cholangiocytes from 1-week bile duct ligated rats, UDCA and TUDCA activate PKC, increase Ca^{2+} and alter the ABAT expression in cholangiocytes, inhibit cholangiocyte growth and secretion.

b. Stimulation of hepatobiliary secretion

The impairment of bile formation, the common disturbance of all forms of cholestasis, results in retention of bile acids and other potentially toxic biliary constituents in the liver.

UDCA stimulates biliary scretion of bile acids and other organic anions (bilirubin glucuronides, glutathione conjugates) and prevents cholestasis induced by hydrophobic bile acids. UDCA stimulates biliary scretion of bile acids in patients with PBC and PSC and decreases serum levels of bilirubin and endogenous bile acids (10,11).

The secretory capacity of hepatocytes is determined by the number and activity of carrier proteins in the apical membrane. UDCA stimulates the expression of transporter proteins for bile acids into the canalicular membrane: bile salt export pump (Bsep) and conjugate export pump (Mrp2). In hepatocytes of mice fed with a diet enriched with UDCA, *Bsep* and *Mrp2* mRNA are up-regulated.

The taurine conjugate of UDCA (TUDCA) stimulates hepatobiliary vesicular exocytosis and apical insertion of transporter proteins, enhances the density of Mrp2. TUDCA induces translocation of Ca^{2+}-sensitive a isoform of PKC (mediator of exocytosis) to hepatocellular membranes and activates PKC (12).

Bile acid secretion may be increased by TUDCA via alternative signaling pathways independent of PKC.

The mitogen-activated protein kinases (MAPKs) include a group of protein kinases that are activated by a variety of signals. Mammalian cells have two major types of MAPK cascades:

- extracellular signal regulated-kinase (ERK1/ERK2);
- stress activated protein kinases (SAPKs) with two distinct subfamilies: c-Jun amino-terminal kinases and p38 MAPK.

The MAPK signaling pathways (mediate signal transduction from the cell surface to the nucleus) involving ERK1/2 and p38 have also been implicated in biliary excretion of bile acids. TUDC-induced increases in bile acid excretion are dependent on ERK 1/2 activation (13). This was accompanied by enhanced insertion of Bsep into the canalicular membrane and by an increase of taurocholic acid excretion.

Another mechanism by which UDCA modulates apical secretion in hepatocytes is phosphorylation/dephosphorylation of transporter proteins (activation/inactivation). The transport capacity of Bsep is increased via PKCα-mediated phosphorylation and inhibited by PKCε (14).

TUDCA modulates PKCα and taurolithocholic acid (cholestatic bile acid) modulates PKCε. UDCA increases Ca^{2+} in cholangio-cytes and induces membrane binding of Ca^{2+}-dependent PKCα. UDCA stimulates biliary ATP secretion, which may induce Ca^{2+}-dependent Cl^- secretion via apical P2Y ATP receptors (15).

c. Protection of hepatocytes against bile acid-induced apoptosis

Bile acids at concentrations of only 25 mmol/l will induce hepatocyte apoptosis. Bile acids induce cell death via ligand-independent death receptor pathways, especially those by the Fas receptor (16).

Apoptosis can be inhibited not only by blocking proapoptotic pathways, but also by accentuating survival signals - intracellular cascades that have evolved to inhibit apoptosis. These survival pathways include cAMP, AKt, nuclear factor KB, MAPK, and phosphatidyl inositol 3-kinase-mediated kinase pathways.

The mechanisms of UDCA cytoprotection remain unclear. With the realization that bile acids induce apoptosis, Rodrigues and Steer showed in a series of seminal observations that UDCA blocks apoptosis by interrupting the classic pathways of apoptosis (17).

Is it possible that UDCA does not simply antagonize toxic bile acids at a biophysical level, but that it elicits survival signals? The answer is yes. Qiao et al have shown, for the first time, that UDCA stimulates the activation of the intracellular MAPK pathway through the activation of the epidermal growth factor receptor (EGFR) (18). This UDCA/EGFR/MAPK pathway blocks bile-acid mediated cytotoxicity and, hence, represents a new bile acid-stimulated survival pathway. Indeed, when the MAPK pathway was blocked with inhibitors, UDCA was toxic. It would appear from these studies that the UDCA/EGFR/MAPK pathway likely inhibits apoptosis by blocking mithocondrial dysfunction, an organelle playing the role of an integrator and amplifies in apoptotic signaling pathways.

UDCA treatment prevents mitochondrial oxidative stress

Oxidative stress plays an important role in cell death and has been linked to the development of cholestatic liver injury. Hydrophobic bile acids stimulate the generation of reactive oxygen species (ROS) in hepatocytes and in liver mitochondria (19). Evidence of oxidative injury has been found in rats receiving intravenously infused hydrophobic bile acids and in the bile duct-ligated rat model of cholestasis. Recently, Sokol et al (20) proposed that hydrophobic bile acids accumulate intracellularly during cholestasis and interfere with normal mitochondrial electron transport, inhibiting the activity of respiratory complexes I and III and consequently reducing adenosine triphosphate synthesis. Mitochondrial dysfunction is widely recognized as a key mechanism leading to apoptosis, particularly through the mitochondrial permeability transition (MPT). Toxic bile salts can induce the opening of MPT pores, and inhibition of MPT prevents bile salt-induced hepatocyte cytotoxicity (21).

Recently UDCA was shown to have *in vitro* antioxidant activity in hepatocytes (22).

Pretreatment with UDCA prevented hydrogen peroxide-induced injury by increasing γ-glutamylcysteine synthetase messenger RNA (mRNA) levels, and, consequently, levels of reduced glutathione (GSH). Furthermore, GSH levels were higher in liver specimens perfused with UDCA than in those perfused with taurocholic acid. This effect is correlated with an increase in methionine S-adenosyl transferase activity.

Another study (23) tried to identify the mechanisms involved in mitochondrial impairment during biliary cirrhosis induced by chronic cholestasis (bile duct ligation) in rats and the mechanisms associated with the protective effects of UDCA against secondary biliary cirrhosis.

Impairment of biliary excretion was accompanied by decreased steady-state hepatic levels of γ-glutamyl cysteine synthetase and γ-cystathionase messenger RNAs. UDCA treatment led to up-regulation of γ-glutamyl cysteine synthetase in animals with secondary biliary cirrhosis and prevented the marked increases in mitochondrial peroxide production and hydroxynonenal-protein adduct production that are observed during chronic cholestasis. A population of damaged and primarily apoptotic hepatocytes characterized by dramatic decreases in mitochondrial cardiolipin levels (cardiolipin may modulate apoptotic processes by inhibiting MPT) and membrane potential as well as phosphatidylserine exposure evolves in secondary biliary cirrhosis. UDCA treatment prevents the growth of this population along with the decreases in mitochondrial cardiolipin levels and membrane potential that are induced by chronic cholestasis.

Mitochondria play a central role in apoptosis. After injury, there is a loss of inner mitochondrial membrane potential and release of factors such as apoptosis-initiating factor and cytochrome C. Released cytochrome C activates caspase 9, which then activates downstream effector caspases, such as caspase 3 and 7.

Recent studies challenge the central role of mitochondria in apoptosis and suggest that some apoptotic signals may by-pass mitochondria to directly activate caspases. A recent study showed that endoplasmic reticulum (ER) stress activates caspase 12 and triggers apoptosis without involvement of mitochondria (24). A variety of agents, including calcium ionophores, inhibitors of glycosylation, toxins and oxidative stress can induce ER stress and lead to cell death.

In vitro studies showed that UDCA prevented apoptosis induced by deoxycholic acid, ethanol, TGF β, Fas ligand and okadaic acid by decreasing mitochondrial depolarization with subsequent inhibition of cytochrome C release and caspase activation. However, although some studies suggested an effect of bile acids on calcium homeostasis (25) there are no data regarding the role of UDCA during endoplasmic reticulum stress-induced apoptosis. In a recent study (26) the authors developed an endoplasmic reticulum stress model of apoptosis in a liver-derived cell line (Huh7) and assessed the role of calcium homeostasis and caspase 12.

Typical morphologic changes of endoplasmic reticulum stress preceded development of apoptotic changes, including DNA fragmentation and cleavage of adenosine diphosphate-ribose polymerase, as well as activation of caspase-3 and 7. These changes were accompanied by procaspase-12 processing TUDCA, abolished markers of endoplasmic reticulum stress, reduces calcium efflux, cascase-12 activation and apoptosis.

Primary biliary cirrhosis

In 1987, an important pilot study was performed by Poupon et al, in which 15 patients with PBC were treated over a period of 2 years with UDCA (27). The study proved the efficacy of UDCA in improving biochemical liver tests as well as the symptoms of the patients.

This study was followed by a number of randomized, double-blind controlled trials which showed an improved evolution of patients treated with UDCA, with fewer deaths and/or referrals for liver transplantation. The largest such study is a multicentric randomized double-blind controlled trial performed by Heathcote et al, in which 222 patients with PBC were treated with UDCA in doses of 13-15 mg/kg/day given once daily (28). Transaminases, alkaline phosphatase, total cholesterol and IgM improved compared to the placebo group, while the rise in serum bilirubin was prevented by UDCA.

Poupon et al conducted a combined analysis of data from the three largest trials, in which a subgroup analysis according to the severity of the disease was also performed (28-31). The study showed that UDCA increases the probability of survival free of transplantation for patients with bilirubin > 1.4 mg/dL. The best results of UDCA were observed in patients with advanced disease (stage IV), likely because of the slow rate of progression of PBC and the relatively short follow-up period. Four independent prognostic factors were also identified in primary biliary cirrhosis: high serum bilirubin level, low serum albumin level, advanced histological stage and high Mayo Risk Score. The risk of liver transplantation was 2.7 times higher in patients with cirrhosis.

More recent studies have shown that UDCA could significantly delay progression of liver fibrosis in the early stages of PBC (32). The probability of remaining free of extensive fibrosis or cirrhosis for patients treated with UDCA was 76% and 61% after 4 and respectively 8 years, compared to 29% and 13% in patients treated with placebo. Similar results were observed in a previous case-control study (33) as well as in a double-blind controlled multicentric trial which included 192 patients (7). In the latter study, Pares et al also showed the favorable effects of UDCA in significantly lowering histological stage and piecemeal necrosis.

Corpechot et al also identified 3 independent factors predicting the development of cirrhosis in patients treated with UDCA (serum bilirubin > 17 mmol/l, albumin < 38 g/l and presence of severe lymphocytic piecemeal necrosis) (32).

In a multivariate analysis performed by Angulo et al the Mayo Risk Score was the only risk factor predictive of esophageal varices in patients treated at least 6 months with UDCA ($p<0.001$) (34). Serum alkaline phosphatase levels after 6 months of UDCA treatment were also found to have prognostic value and can be used as a marker of response to UDCA after treatment.

Leuschner et al performed a study that showed that high baseline serum alkaline phosphatase levels are more likely to predict treatment failure (35).

The fact that UDCA administration delays referral of PBC patients to liver transplantation generated fears that these patients could have a poorer post-transplant evolution. However, a retrospective study conducted by Heathcote et al (36) comparing the evolution of patients who had received UDCA pretransplant compared to placebo clearly showed that UDCA did not increase the risk of death, infection or rejection within the first year of transplantation.

Lindor et al also showed that UDCA could decrease the rate of development of esophageal varices (37). It has also been shown that UDCA lowers serum cholesterol levels, directly related to the improvement of serum bilirubin during therapy and inversely related to the initial level of serum cholesterol (38). However, UDCA does not seem to improve the autoimmune diseases associated with primary biliary cirrhosis (39).

In a study performed by Angulo et al (40), three dosing regimens of UDCA were administered to PBC patients: 5-7, 13-15 and 23-25 mg/kg/day. The authors remarked similar efficacy regarding biochemical and Mayo Risk Score improvement for 13-15 mg/kg/day and 23-25 mg/kg/day, and both these regimens offered significantly better results than the 5-7 mg/kg/day dosing. Regarding safety of the different doses, most side effects appeared in the low-dose group, suggesting that these adverse events were not dose-related.

Primary sclerosing cholangitis

In a randomized, placebo-controlled trial conducted by Lindor et al (41) the effect of 13-15 mg/kg/day of UDCA was evaluated in 105 patients with PSC over a mean follow-up period of 2.2 years. The study demonstrated statistically significant improvement in the serum levels of alkaline phosphatase, bilirubin, albumin and ASAT of patients treated with UDCA. However, UDCA was not able to prevent histological progression in this group of patients. Furthermore, the time to treatment failure and the time to liver transplantation were similar in the two patient groups.

Van Hoogstraten et al performed a randomized controlled trial (42) in which they compared single daily dose versus multiple daily dosing of UDCA in patients with PSC, with no significant differences between the two dosing regimens. Both regimens resulted in similar decreases of serum alkaline phosphatase and had no effect on serum bilirubin and IgG levels or on the histological stage.

High doses of UDCA in PSC patients were evaluated in two studies. Mitchell et al (43) randomized 26 patients to receive either 20 mg/kg/day UDCA or placebo with a follow-up of two years. The authors noted in the UDCA group a biochemical response (decrease of alkaline phosphatase and GGT) as well as histological response, with less progression in the disease stage. In the second study conducted by Harnois et al (44), 25-30 mg/kg/day of UDCA was administered to 30 patients with PSC, who were then followed-up for one year. This study also proved biochemical improvement (decrease in alkaline phosphatase, ASAT, albumin and bilirubin levels). The Mayo prognostic model showed that in these patients expected mortality at 4 years was significantly lower compared to that noticed in patients who had received placebo in a study performed by Lindor et al: 11% vs. 17% (41).

The beneficial effects of UDCA in patients that associated PSC with ulcerative colitis were noted in a study conducted by Tung et al (45), with a lower prevalence of high grade colonic dysplasia in patients treated with UDCA.

The effects of high doses of UDCA in PSC are also being evaluated in a large scale randomized multicenter trial which is currently underway.

Intrahepatic cholestasis of pregnancy

This cholestatic disorder affects pregnant women during the III-rd trimester and responds to UDCA therapy. In small controlled trials, UDCA improved pruritus and hepatic biochemical tests, including bilirubin and aminotransferases and decreased the number of premature births (46). An uncontrolled trial showed that an increase of the dose of UDCA from 1.5 to 2 gr/day (20-25 mg/kg/day) improves hepatic biochemical tests such as aminotransferases and serum bilirubin in intrahepatic cholestasis of pregnancy. A consequence on the evolution of the mother or fetus outcome remains to be proven.

No adverse effects of UDCA were reported in children or in women treated during pregnancy. UDCA may be considered to be a safe treatment in this disease, but additional controlled trials are necessary before this drug can be recommended on a large scale in intrahepatic cholestasis of pregnancy.

Liver disease in cystic fibrosis

This genetic disorder is caused by a mutation in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene, which results in the secretion of a viscous bile. This may lead to the formation of plugs in the biliary ducts, biliary obstruction, focal biliary fibrosis and focal biliary cirrhosis.

In a randomized, double-blind, placebo-controlled trial performed over a period of one year, UDCA improved biochemical markers of cholestasis, nutritional status and the general condition of patients (47). Histological improvement was also reported (48). The prognostic significance of these improvements remains however unclear. A higher dose of UDCA (20 mg/kg/day) is much better than a low dose (10 mg/kg/day) due to the fact that intestinal absorption of UDCA and as a consequence, enrichment of the bile with UDCA is modified when pancreatic failure is present (49).

UDCA appears as an efficient and safe treatment in cholestatic liver disease that develops in cystic fibrosis. However, its effect on survival has not yet been proven.

Progressive familial intrahepatic cholestasis (PFIC)

PFIC represents a group of autosomal recessive hereditary diseases that appear in childhood, in which cholestasis is present starting from the neonatal period or the first years of life and which leads to death through liver failure during childhood or adolescence. This is caused by imperfect transporters of the canalicular membrane, namely FIC 1 (PFIC 1), BSEP (PFIC 2) and MDR (PFIC 3). While children wih PFIC 1 or PFIC 2 are characterized by normal γ-glutamyl transpeptidase (GGT) serum levels, children with PFIC 3 have very elevated GGT levels.

Patients with PFIC were treated with UDCA (20-30 mg/kg/day) over a period ranging from 2 to 4 years (50). Thirty-six children presented normal GGT levels while 13 presented elevated GGT. In the whole group, aminotransferases and GGT decreased significantly and the nutritional status improved. Hepatic functional tests normalized in 40% of cases and improved in 20-30% of patients. No adverse effects of UDCA were reported. The factors responsible for this effect of UDCA remain unclear. The response may be related to the type and/or position of the mutation of the responsive gene, to the residual activity of BSEP or FIC in patients with normal GGT. In patients with elevated GGT with a partial defect of MDR3 and residual concentrations of phospholipids in the bile, UDCA administration may be sufficient to reduce toxicity of bile acids in the bile to the critical limit. In contrast, nonresponders may present a complete defect in phospholipid secretion.

Graft versus host (chronic form)

Liver injury in this disease may cause cholestasis. A randomized placebo-controlled trial showed that prophylactic administration of UDCA in patients who suffered bone marrow transplantation and were prepared with busulfan and cyclophosphamid decreases the incidence of hepatic complications (51).

Drugs and parenteral nutrition - induced cholestasis

Small series of cases suggest that UDCA therapy may be beneficial in these situations (1).

Conclusion

Although UDCA has been used in the treatment of cholestatic liver diseases for over a decade, the main mechanisms of its anticholestatic effects have just recently been revealed. Future efforts will focus on defining the diseases with indication of UDCA therapy, the optimal dosing regimen, as well as on the clarification of its mechanisms of action. Among these, the suggestion that UDCA induces P450 3A4 cytochrome – enzyme which metabolizes bile acids, drugs and cholesterol and the speculation that UDCA lowers the cholangiocellular concentration of hydrophobic bile acids seem to present a special interest.

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