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Ursodeoxycholic Acid (UDCA) in Biliary Diseases: A Clinical Review

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Author's contribution

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Review Article

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ABSTRACT

Ursodeoxycholic acid (UDCA) is an established and accepted treatment of biliary diseases such as gallstones and primary biliary cirrhosis. Mechanisms of action of UDCA are not so far completely elucidated. UDCA tablets are indicated for the dissolution of small to medium sized radiolucent, cholesterol-rich gall-stones in patients with a functioning gall bladderand in the treatment of primary biliary cirrhosis (PBC). The Food and Drug Administration's Gastrointestinal Drugs Advisory Committee has stated that UDCA is safe and effective for the treatment of primary biliary cirrhosis. More recent Meta-analysis have cast doubt on the real impact of UDCA in patients with PBC. However more recent articles and systematic reviews have pointed out that the risk of death or liver transplantation was reduced by 32% in PBC patients treated with UDCA compared to placebo. In this review we summarized the principal evidence of efficacy of UDCA in the treatment of biliary diseases. UDCA remains so far a relevant pharmacological treatment in biliary diseases.

Keywords: Ursodeoxycholic; biliary diseases; review.

1. INTRODUCTION

Ursodeoxycholic acid (UDCA; 3, 7-dihydroxy-5-cholanic acid) (Fig. 1.) is a hydrophilic bileacid that is increasingly used for the treatment of various cholestatic disorders [1]. It is normally present in human bile, albeit in a low concentration of only about 3% of total bile

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acids [2]. UDCA is used in several biliary diseases [3] from bile duct stone to the treatment of cholestasis in parenteral nutrition patients and in the treatment of primary biliary cirrhosis [4]. UDCA is also used in the prophylaxis of gallstones during rapid weight reduction [5]. A Cochrane review [6] has been quite recently published in order to evaluate if UDCA has any beneficial effect in primary biliary cirrhosis patients included 16 randomized clinical trials with a total of 1447 patients. The primary outcome measures were mortality and mortality or liver transplantation. Although treatment with UDCA showed a reduction in liver biochemistry, jaundice, and ascites, it did not decrease mortality or liver transplantation. More recent articles and systematic reviews have pointed out in PBC UDCA treatment significantly reduces the risk of death or liver transplantation in comparison with placebo. UDCA is the only FDA-approved medical treatment for PBC and should be administered at a recommended dose of 13-15mg/kg/day [7]. Up to 66% of patients with PBC respond to this treatment [8]. UDCA tablets are mainly indicated in the treatment of primary biliary cirrhosis (PBC) and for the dissolution of small to medium sized radiolucent, cholesterol-rich gall-stones in patients with a functioning gall bladder.

2. PHARMACOLOGY OF UDCA

Ursodeoxycholic acid (UDCA) is a derivative ofchenodeoxycholic acid [9]. Conversion of chenodeoxycholic acid into ursodeoxycholic acid occurs in two stages via 7- ketolithocholic acid. UDCA acid is a secondary bile acid (produced in the gut) as well as a tertiary bile acid (produced in the liver) [10]. Oral bioavalability of UDCA is quite good: about 30-60% of orally administered UDCA is absorbed [11]. Although poorly water soluble in the protonated form, unconjugated UDCA acid is absorbed along the entire length of the jejunum and ileum by non-ionic passive diffusion8; about 20% may be absorbed in the colon. The absorption of free UDCA is facilitated by prior solubilisation by other bile acids. Hence, it is advisable that UDCA acid should be taken with a meal that induces gallbladder contraction [12]. The absorption of UDCA 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 UDCA. The high first-pass metabolism (70%) results in low blood levels of UDCA after an oral dose. The half-life of UDCA is 3.6 to 5.8 days in humans [13].UDCA may act by several mechanisms, all of which are poorly understood [14]. The most obvious one is a relative decrease in the toxic hydrophobic bile acids. The major mechanism by which UDCA achieve bile desaturation is through a decrease in secretion of cholesterol into the bile [15]. UDCA reduces cholesterol absorption, suppresses liver cholesterol synthesis and does not inhibit bile acid synthesis [16]. UDCA is able to alter bile composition from supersaturated to unsaturated [17]. Ursodiol also promotes the formation of liquid cholesterol crystal complexes which enhance removal of the cholesterol from the gallbladder into the intestine to be expelled It has been suggested that the hydrophilic nature of UDCA confers cytoprotection in necro-inflammatory diseases of the liver [18]. 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.

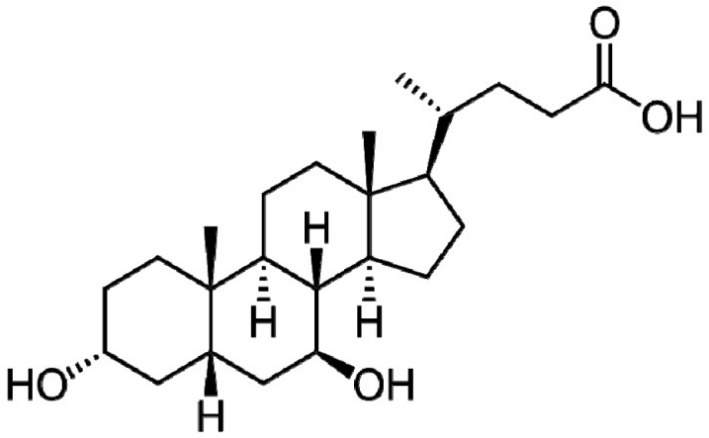

Fig. 1. Molecular formula of UDCA

3. UDCA IN GALL STONES

Cholesterol gallstone disease is a common clinical condition influenced by genetic factors, increasing age, female gender and metabolic factors [19]. Laparoscopic cholecystectomy is currently considered the gold standard in treating patients with symptomatic gallstones [20]. Drugs with cholesterol-lowering properties which inhibit cholesterol synthesis or intestinal cholesterol absorption or drugs acting on specific nuclear receptors involved in cholesterol and bile acid homeostasis, might be proposed as additional approaches for treating cholesterol gallstones [21]. UDCA is indicated in chemodissolution of bile duct stone [21]. UDCA is more hydrophilic and less toxic than CDCA and is currently employed for oral litholysis of small cholesterol gallstones in patients with a functioning gallbladder [22]. This bile acid, in a dose of 10-14 mg/kg per day, increases its proportion in the bile acid pool (it originally accounts for less than 8%-10% of the biliary bile acid pool in healthy subjects), inducing a decreased hepatic secretion of biliary cholesterol and the formation of unsaturated gallbladder bile. The fine mechanisms involved in UDCA-induced dissolution of cholesterol stones are rather complex [23]. The so-called ternary phase diagram is used to explain the molecular effects of UDCA on bile composition and cholesterol solubility. A bedtime administration of UDCA or TUDCA, is recommended since it maintains hepatic bile acid secretion rate overnight, thus reducing secretion of supersaturated bile and increasing the dissolution rate [21]. The hydrophilic bile acid UDCA is also able to act as alitholytic agent through the reduction of intestinal cholesterol absorption and as a possible “prokinetic” agent capable of ameliorating postprandial gallbladder emptying as suggested by observations in vitro on isolated gallbladder smooth muscle strips from both animals and gallstone patients [24]. The improvement of gallbladder smooth muscle contractility probably also results from the prevention of the impairment of smooth muscle contractility induced by the more hydrophobic and toxic deoxycholate [25]. UDCA therefore could be viewed as the medical treatment of choice for dissolution of cholesterol gallstones [26]. So far, there is no evidence that UDCA could replace or reduce the need for cholecystectomy. However, the drug should be considered an attractive alternative to surgery in selected patients and should be considered over chenodiol when drug therapy for gallstones is indicated. In this clinical indication the recommended oral dosage of UDCA for the treatment of radiolucent, non-calcified gallstones of less than 20 mm in diameter is 8 to 10 milligrams/kilogram/day in

2 to 3 divided doses [27]. In general clinical symptoms with gallstone disease are reduced after 3 months of UDCA treatment [28].

4. UDCA IN PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterized by progressive destruction of intrahepatic bile ducts with cholestasis, portal inflammation and fibrosis which may lead to cirrhosis, to its complications, and eventually to liver transplantation or death [29]. This autoimmune illness has a familial predisposition, in which even unaffected family members may have immunologic abnormalities, especially an increased serum immunoglobulin M (IgM) and an association with human leucocyte antigen (HLA)-DR8 [30]. The diagnosis of PBC is currently based on three criteria [31]: the presence of AMA and AMA-M2 in serum which is highly specific for the disease, elevation of biochemical indices of cholestasis for more than 6 months, and histological features in the liver that are indicative of the diagnosis [32]. The rationale for the use of UDCA in the treatment of PBC depends on its capability in displacing and diluting hepatotoxic bile acids from the bile acid pool. It is well known that in cholestatic conditions, endogenous bile acids are retained within hepatocytes, thus leading to the progressive deterioration of liver function [33]. Also fibrates are used in this condition even if so far there are not conclusive data on this indication [34]. The only accepted treatment for PBC is UDCA [35] that actually may delay but not completely cure or halt the progression of the disease. Clinical studies have shown that the effective UDCA dose in this clinical setting is 13 to 15 milligrams/kilogram/day, in two to four divided doses [36]. UDCA is in fact considered the first-line therapy for PBC. The rationale for the use of UDCA in the treatment of PBC depends on its ability in displacing and / or diluting detergent and hepatotoxic bile acids from the bile acid pool [37]. It is well known that in cholestatic conditions, endogenous bile acids are retained within hepatocytes, thus leading to the progressive deterioration of liver function [38]. The beneficial effects of UDCA on indices of liver dysfunction have been attributed to its physicochemical properties, since UDCA is very hydrophilic and therefore non-toxic to biological membranes [39]. Immunomodulatory effects of UDCA have been also described [40]. A number of randomized controlled studies have been conducted to evaluate UDCA efficacy [41]. In all studies UDCA was well tolerated since no relevant side effects were reported. In all studies a significant improvement of serum liver enzymes markers of cholestasis and cytolysis occurred. Serum concentrations of bilirubin, the most important prognostic marker of the disease, were reduced by UDCA administration [42]. A consistent reduction of IgM, which is an immunological marker of PBC was also reported [43]. UDCA improves both serum liver biochemistries and histology of PBC patients [44]. UDCA administered over a range of 9 months to 2 years has been found to significantly improve liver function tests in patients with primary biliary cirrhosis [45]; UDCA does not act on the aetiology of the disease but reverses the detrimental effects of the retention of endogenous bile acids within the liver. However, some studies have shown no benefit in survival outcomes with UDCA therapy [46] and two meta-analyses [47,48] have demonstrated that actually there was no survival difference between UDCA-treated patients compared to place-treated patients [5,49]. In particular Triatos et al. [39] evaluating at total of 8 trials found that here was no significant difference in mortality, in pruritus, in fatigue, in cholangiocarcinoma and in histology stage progression in patients treated with UDCA in comparison with placebo. On the contrary a significant improvement of survival could be recorded only in patients with serum bilirubin higher than 1.4 mg/dL at baseline [50]. These two meta-analyses included studies of short duration and those that used an inadequate dose of UDCA. A more recent meta-analysis [51] addressed these concerns and found that the risk of death or liver transplantation was reduced by 32% in patients treated with UDCA compared to placebo [52]. A subsequent combined analysis of the three largest clinical trials

showed that UDCA prolongs survival free of liver transplantation [49]. Long-term treatment with UDCA appears to slow disease progression and has altered the naturalhistory of PBC [53]. Boberg [54] in a prospective long term observational study carried out in 182 PBC patients treated with UDCA demonstrated that UDCA oral treatment is a dominant strategy conferring reduced morbidity and mortality, as well as cost savings, compared with standard therapy. These data therefore reinforce the clinical utility of UDCA in PBC treatment strategy [49] even if UDCA treatment probably could have a significant benefit in patients with early disease stages. The benefit could be limited in those with already cirrhosis or more advance disease. Recently Lens et al. [55] have shown that combination treatment of bezafibrate and UDCA is associated with marked decrease or normalization of alkaline phosphatase as early as 3 months in patients with PBC.

5. CONCLUSION

UDCA could be yet considered a first-line pharmacological treatment for biliary diseases. UDCA tablets are indicated in the treatment of primary biliary cirrhosis (PBC) and for the dissolution of small to medium sized radiolucent, cholesterol-rich gall-stones in patients with a functioning gall bladder. UDCA remains a relevant pharmacological treatment in biliary diseases.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

The author reports no conflict of interest.

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