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EDITORIAL

Ursodeoxycholic acid therapy in gallbladder disease, a story not yet completed

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Abstract

Gallstone disease represents an important issue in the healthcare system. The principal non-invasive non-surgical medical treatment for cholesterol gallstones is still represented by oral litholysis with bile acids. The first successful and documented dissolution of cholesterol gallstones was achieved in 1972. Since then a large number of investigators all over the world, have been dedicated in biochemical and clinical studies on ursodeoxycholic acid (UDCA), demonstrating its extreme versatility. This editorial is aimed to provide a brief review of recent developments in UDCA use, current indications for its use and, the more recent advances in understanding its effects in terms of an anti-inflammatory drug.

Key words: Gallbladder; Cholesterol gallstones; Ursodeoxycholic acid

Core tip: Ursodeoxycholic acid can be considered one of the less expensive, best tested and safest of the drugs currently available. This editorial is aimed to provide a brief review of the principal non-invasive non-surgical medical treatments for cholesterol gallstones. Based on the literature and on our experimental and clinical works we try to summarize the recent developments in ursodeoxycholic acid use, current indications for its use and the more recent advances in understanding its effects in terms of an anti-inflammatory drug. For these reasons, the story would not appear to end herewith but deserves further attention and investigation.

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INTRODUCTION

Gallstone disease still represents a relevant issue for the healthcare system and one of the most common and costly of all digestive diseases if we consider the number of cholecystectomies, which are performed annually all over the world, and the hospital admission rate for complicated gallstone disease[1,2]. A marked variation in overall gallstone prevalence between the different ethnic populations has been reported; native populations from North and South America represent the groups at the highest risk in the world. Symptoms occur in approximately 20% of patients, and this subgroup is at the highest risk of developing serious complications from gallstone disease. These complications can range from simple to severe recurrent biliary colic, ascending cholangitis and/or pancreatitis[3].

Gallstone disease is a complex disorder where both

environmental and genetic factors contribute to the susceptibility to the disease. Risk factors include age, gender, race, parity, dietary factors. A family history of gallstones has also been identified as a risk factor suggesting that genetics play a role in gallstone formation. Genetic factors seems to be responsible for at least 30% of symptomatic gallstone disease[4]. Furthermore, as in atherosclerosis, the risk of cholesterol gallstone disease increases with obesity, type 2 diabetes, insulin resistance and dyslipidaemia, conditions associated with the metabolic syndrome[1,5].

Gallstones are classified as cholesterol and pigment stones. More than 90% of gallstones consist mainly of cholesterol and are formed within the gallbladder[3].

TREATMENT OF GALLSTONE DISEASE

A physician of the Byzantine Empire first described calculi in the human liver, but the earliest evidence of human gallstones is represented by the finding of 30 stones in the intact gallbladder of a mummified Egyptian priestess from around 1500 BC. In the past, a multiplicity of treatments have been used to attempt gallstone dissolution, including prayer, magic, herbs and potions[6].

The modern medical therapeutic management of gallstone disease depends primarily upon the clinical stage: asymptomatic, symptomatic (typical biliary colic pain), and complicated disease.

Asymptomatic gallstones rarely warrant treatment, since they generally have a benign natural course; the progression to symptomatic disease is relatively low, ranging from 10% to 25%. The majority of patients rarely develop gallstone-related complications without having at least one episode of biliary pain. In the pre-laparoscopy era, cholecystectomy was generally performed for symptomatic disease. The minimally invasive laparoscopic cholecystectomy refuelled the controversies regarding the optimal management of asymptomatic or silent gallstones, but most experts agree that the majority of patients should be managed by observation alone (expectant management)[7]. According to the National Institutes of Health Consensus Conference report "the availability of laparoscopic cholecystectomy should not expand the indications for gallbladder removal"[8]. Moreover, follow-up studies on a total of 279 patients with silent gallstone disease reported that the natural history of asymptomatic gallstones is benign and only 20% of these patients developed pain or complications within 24 years[9].

Symptomatic gallstone disease or acute cholecystitis are the primary indications for cholecystectomy that is currently considered the "gold standard" for the treatment of gallstone disease. Cholecystectomy is one of the most commonly performed abdominal surgical procedures, the first carried out in 1882 by Carl von Langenbuch[6]. The credit of establishing surgery of the gallbladder on a firm footing belongs to Langenbuch. The safety and success of this operation was soon established. Laparoscopic cholecystectomy is a minimally invasive surgical technique that was first performed in France, in 1987, and, in the United States, in 1988. This technique has now replaced open cholecystectomy as first-choice treatment for selected types of patients and represents one of the safer surgical procedures[8].

Non-surgical management of gallstones has been widely investigated over the last few decades, including gallstone dissolution both by mechanical and biochemical means[10].

Since its introduction, in 1985, in Germany, extracorporeal shockwave lithotripsy (ESWL) had been shown to be useful for fragmentation of bile duct stones that were not extractable endoscopically and its efficacy was soon established for selected patients at high surgical risk (> 70 years old, high morbidity and mortality rates) presenting gallstone disease (solitary radiolucent calculi < 2 cm in diameter)[11]. ESWL adopts focused shock waves produced by electromagnetic or ultrasound sources to fragment gallstones, but its efficacy depends upon the amount of energy delivered to the stone as well as the emptying and fasting volumes of the gallbladder[6]. Since its introduction in gastroenterology, ESWL had been considered as an adjuvant of oral bile acid in the treatment of gallstones, since it increases the surface for bile salt action fragmenting the stones into smaller particles. The major disadvantage of ESWL is the high post-dissolution recurrence rate (being 11%-26% for a 24-mo period), which had always raised the issue of cost-effectiveness[12]. For this reason, at present, even if advances have been made in lithotripsy technology (*i.e.*, the introduction of pulverization), none of the ESWL machines have been approved by the Food and Drug Administration (FDA) for routine clinical use in the United States, therefore this technique is no longer widely used, except in some European countries[8]. In the early period of the first use of ESWL, much interest was aroused by the application of contact dissolution agents, even if considerably less experience had been recorded. It involved direct entry of a potent cholesterol solvent (such as methyl tertiary-butyl ether, MTBE), either instilled directly into the gallbladder or into the bile duct following endoscopic intubation. Cholesterol prevalent stones could be cleared within hours to days. Interest in this method was soon lost due to the potential side-effects and was therefore limited to patients that were at high surgical risk[13] .

The principal non-invasive non-surgical medical treatment for cholesterol gallstones is still represented by oral litholysis with bile acids[14]. The first successful and documented dissolution of cholesterol gallstones was achieved in 1972 by oral administration of chenodeoxycholic acid (CDCA), a primary trihydroxy bile acid[15]. The use of CDCA due to a dose-dependent increase in aminotransferases, to an increase in serum low-density lipoprotein cholesterol and the development of bile salt-induced diarrhoea, raised concerns[15]. Since the more hydrophilic UDCA appeared to be as effective in gallstone dissolution but practically devoid of side-effects, it rapidly replaced CDCA and represents the most widely recorded experience in the literature[16].

Recently some studies have suggested the possibility of using, as therapeutic agents for gallstone disease, cholesterol-lowering agents such as statins and ezetimibe that inhibit hepatic cholesterol synthesis or reduce the absorption of cholesterol in the small intestine, alone or in combination with other forms of treatment[17-21]. Despite some promising initial data in the literature, there are still some conflicting results, thus suggesting that UDCA is the most suitable of medical treatments for gallstone disease.

URSODEOXYCHOLIC ACID

The use of UDCA in the treatment of liver diseases dates back to the traditional Chinese medicine during the Tang Dynasty. For centuries, the Chinese drug "*shorea spp.*", derived from the bile of adult black bears, has been used to cure various hepatobiliary disorders. Only at the beginning of the 20th century, was UDCA identified from polar bear bile by Hammarsten[22], a swedish research worker, who named this uncharacterized bile acid as ursocholeinic acid. The bile acid he identified was actually CDCA. It is anecdotally said that he ran out of the sample during the course of purification and abandoned its crystallization. Twenty years later, in 1927, Shoda, from Okayama University, isolated UDCA from bear bile imported from China, succeeded in crystallizing it and then called it by its present name, *i.e.*, Urso-deoxycholic ("*urso*", bear in Latin), being the predominant bile acid in bears[22].

Until Makino *et al*[22] clearly demonstrated that treatment with UDCA resulted in dissolution of cholesterol gallstones, UDCA was predominantly used in Japan as a liver tonic being administered in doses that were too small to have any significant therapeutic effect. Thereafter its use spread worldwide following further confirmation of its effectiveness and safety[23].

From the time of marketing to the present day, a large number of investigators all over the world have been involved in biochemical. At present, and clinical studies on UDCA, demonstrating its extreme versatility. UDCA can be used as a therapeutic tool in cholestatic liver diseases, being currently considered the only medical treatment officially approved by the United States FDA, to treat primary biliary cirrhosis. It can also be a therapeutic tool for non-cholestatic diseases and even for non-hepatobiliary ones[24]. For example, it appears to exert an anti-proliferative effect in terms of colon cancer prophylaxis and adenoma recurrence, an immunomodulating effect in patients affected by AIDS and it would appear to play a protective role in idiopathic recurrent pancreatitis[25]. Finally, UDCA, thanks to its biochemical structure, can penetrate the blood-brain barrier, so in the future it may be found an application of UDCA as a cell membrane stabilizer in central nervous system disorders[25].

Despite the extensive evidence accumulated regarding the possible use of UDCA in various types of diseases, the largest amount of evidence still remains the beneficial effect of UDCA in dissolution of cholesterol gallstones.

UDCA IN GALLSTONE DISEASE

UDCA, in pharmacological doses, markedly decreases biliary cholesterol saturation by 40%-60%, by inhibition of cholesterol absorption in the intestine, and cholesterol secretion into bile as indicated by a decrease in the cholesterol fraction of biliary lipids[24]. Moreover, it is well known that UDCA decreases toxicity of bile acids which can damage cell membranes and cause cholestasis, through different means of action: by inhibition of hydrophobic endogenous bile acids absorption from the small intestine, by exerting a choleretic function that induces dilution of endogenous bile salts in the bile ducts and by protecting hepatocytes against toxic bile acids[25,26].

Since Makino *et al*[22] first reported gallstone dissolution with UDCA, it has been used above all in the treatment of gallbladder cholesterol stones as an alternative to cholecystectomy[24,27]. Although gallstones are mainly composed of cholesterol, only a small number of patients (< 10% of total) can be treated with systemic dissolution therapy using UDCA[16]. Candidates for UDCA treatment should have cholesterol-enriched non-calcified gallstones < 20 mm in diameter and a patent cystic duct. The recommended dose of UDCA for gallbladder stones is 8-10 mg/kg per day, larger doses do not offer additional benefits. A dissolution rate of 30%-60% (about 1 mm decrease in stone diameter per mo) has been reported, although the initial gallstone diameter has been shown to be the most important factor affecting the dissolution rate[27-29]. A clinical study demonstrated complete disappearance of small stones (< 5 mm) with UDCA treatment after 6 mo (90% in approximately 90% of cases)[16]. Following complete dissolution, UDCA should be continued for another 3 mo in order to confirm decomposition of microscopic stones that may not be detected by ultrasonography. Absence of, or minimal, change in gallstone diameter within 6 to 12 mo of UDCA treatment represents a poor prognostic sign for dissolution[28]. The chance of reducing, by means of dissolution the size of large (> 20 mm diameter) or multiple stones, is very poor (less than 40%-50% after 1 year of treatment)[16].

Biliary sludge has been considered another therapeutic target of UDCA. Sludge formation in the biliary system can be accelerated for example by rapid weight loss, pregnancy, total parenteral nutrition and solid organ transplantation. The beneficial effect of UDCA in this condition has been shown in a clinical study in which idiopathic acute pancreatitis has been related to microscopic gallstones or biliary sludge. In this study UDCA administration within 3 to 6 mo prevented gallstone recurrence and more episodes of pancreatitis over a follow-up of 44 mo[28].

The greater limit of UDCA therapy for gallstone dissolution can be considered the high recurrence rate. Several studies have reported a recurrence rate of 30%-50% at 5 years and 50%-70% at 12 years, after successful treatment, especially in patients with multiple gallstones[16,28,29].

For these reasons, the therapeutic effect of UDCA in patients with symptomatic gallbladder stones has been controversial over the last few decades but the usefulness of this bile acid, as a therapeutic tool, has been successively reconsidered not only for its dissolution capacity, but also for the anti-inflammatory effect. A long-term follow-up study on UDCA treatment showed a significant decrease in the incidence of gallstone disease complications. In particular, this study showed that UDCA treatment in patients with symptomatic gallstones reduced the incidence of biliary pain and acute cholecystitis compared with no treatment over an 18-year period[30]. Interestingly, this therapeutic effect was independent of gallstone dissolution suggesting that UDCA could achieve these effects by restoring the normal gallbladder environment which more recent studies, on gallstone disease, have clearly shown to be characterized by an inflammatory status. A more recent 3-mo randomized placebo-controlled study showed that UDCA did not exert any beneficial effect on biliary pain or complications[31]. It should be pointed out that, there are significant differences in the recurrence rates of biliary pain and need for cholecystectomy between these two studies. Tomida *et al*[30] reported recurrence rates of < 10% in those patients on UDCA compared to 40% in those on placebo after 4 years. In contrast, in the most recent clinical trial, the need for cholecystectomy after 100 d on UDCA or placebo reached almost 75%[31]. These differences suggest that UDCA may not be effective in patients with more advanced chronic inflammatory gallbladder disease. Our earlier findings showing that UDCA treatment restores gallbladder muscle functions and reduces the biochemical markers of oxidative stress and inflammation may support, and partially explain, the beneficial effects in patients with symptomatic gallbladder stones which were independent of gallstone dissolution[32].

A series of *in vitro* studies have investigated the anti-inflammatory effect of UDCA. Cystic duct ligation in guinea pigs does not to cause acute cholecystitis unless the bile is lithogenic with cholesterol and concentrated bile is injected into the gallbladder[33,34]. Guinea pigs submitted to common bile duct ligation develop acute cholecystitis within 2-3 d together with biochemical and pathologic changes similar to those found in human acute cholecystitis, with or without gallstones[34,35]. Gallbladder muscle cells present increased levels of reactive oxygen species (ROS), lipid peroxidation and prostaglandin E2 (PGE2) levels, their response to cholecystokinin (CCK-8), PGE2 and potassium chloride being impaired, and associated with a significant reduction in receptor binding of these ligands[34]. These abnormalities were reproduced by treating normal human muscle cells with H_2O_2 or with hydrophobic bile acids (tauro-chenodeoxycholic acid, TCDC) and are prevented by pre-treatment with PGE_2 or with the free radical scavenger catalase suggesting that hydrophobic bile acids damage receptors and calcium channels of gallbladder muscle cells by stimulating the generation of ROS[36,37]. Interestingly, *in vitro* studies have shown that muscle cells pre-incubated with UDCA prevent TCDC-induced muscle cell damage and ROS production[36]. This specific beneficial effect of UDCA has been confirmed by the previously mentioned double blind, randomized 4-wk, study, carried out by our group, comparing the effects of UDCA with those of placebo in patients scheduled to undergo cholecystectomy for symptomatic gallbladder stones. In particular, this study revealed that pre-treatment with UDCA restores the normal contraction of gallbladder muscle cells by reducing cholesterol content in the plasma membranes and levels of H_2O_2, lipid per-oxidation, platelet-activating factor-like lipids as well as the production of PGE2 and catalase activity[32]. These results are consistent with data reported in a non-randomized study showing improved gallbladder muscle strip contraction in patients treated with UDCA for 3 wk compared to patients not receiving treatment[38].

These data support the hypothesis that lithogenic bile containing excess cholesterol creates a permissive environment in the gallbladders altering the normal balance between hydrophobic bile acids and gallbladder protective mechanisms. Bile acids stimulate the formation of reactive oxygen species, capable of initiating inflammatory processes and cholecystitis. Thus UDCA, by reducing the excess cholesterol and "neutralizing" the hydrophobic bile acids, restores the balance between aggressive biliary factors and gallbladder protective mechanisms[32].

Hydrophobic bile acids, such as chenodeoxycholic and deoxycholic acid, have also been demonstrated to have a toxic effect on the liver mainly by the generation of reactive oxygen species[39,40]. In particular, hydrophobic bile acids, following hepatic retention, may affect not only the hepatocytes but also the resident macrophages (*i.e.*, Küpffer cells) which generate reactive oxygen species and increase the level of oxidative stress[41]. Therapeutic concentrations of UDCA enrich the bile acid pool with UDCA resulting in a pool profile shifting from hydrophobicity to hydrophilicity[42]. UDCA administration has been shown to prevent and reduce the hydrophobic bile acid damage in the liver; indeed, in addition to displacement of the hydrophobic bile acids, UDCA appears to exert a beneficial effect by preventing hydrophobic bile acid-induced stimulation of macrophage oxidative processes[41].

A study from our group suggests that UDCA appears to exert a prophylactic action on the effects of hydrophobic bile acids on the macrophage oxidative processes in the gallbladder. Data emerging from this study reveal the occurrence, in gallbladders surgically

removed from patients with cholesterol gallstones, of an increased number of macrophages in the muscle layer when compared to the normal gallbladder. Of interest, this double blind randomised 4-wk study comparing the effects of UDCA with those of placebo in patients with symptomatic gallbladder stones, scheduled to undergo cholecystectomy, showed that this hydrophilic bile acid leads to a decrease in the number of activated macrophages in the muscle layer and to the reduced production of PGE2 in the gallbladder muscle[43]. PGs are catalytic products of cyclooxygenase-2 (COX2) and are well-known modulators of gastro-intestinal smooth muscle function[44,45]. In our study, COX2 was mainly expressed in the muscle by macrophages and a direct correlation was found between the number of the COX2 and the CD68 positive cells which represent the macrophages. Although a minor contribution of other cell types, such as mast cells and muscle cells, in which PGE2 production contributes to the mechanisms of cytoprotection[46], cannot be definitely excluded, our findings support the hypothesis that another anti-inflammatory effect of UDCA could result from the decrease in the number of activated macrophages which are the main source of PG production. This finding adds another evidence of the anti-inflammatory effect of this hydrophilic bile acid.

CONCLUSION

The large number of studies concerning the UDCA in gallbladder and liver disease published in the literature, over the last few years, clearly indicates the beneficial effect of this bile acid, supported by the more recent advances in the understanding of its effects in terms of anti-inflammatory drug.

Indeed, as only a small number of patients can benefit from UDCA, in terms of dissolution therapy, its specific beneficial effect is related also to prevention of complications in symptomatic gallstone carriers, which is independent from stone dissolution. In our opinion this hydrophilic bile acid could be an alternative therapeutic approach in high surgical risk patients with symptomatic gallbladder stones.

Furthermore, UDCA is one of the less expensive, best tested and safest drugs currently available. For these reasons, the story would not appear to end herewith but deserves further attention and investigation.

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