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Review Article

Ursodeoxycholic Acid in Gallbladder Stone: A Narrative Review

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Abstract:

Ursodeoxycholic acid (UDCA) is a bile acid that can help dissolve certain types of gallstones, specifically cholesterol gallstones. It works by reducing cholesterol production in the liver and increasing bile acids in the bile, which aids in dissolving the stones over time. UDCA therapy typically involves oral medication in tablet or capsule form, and the dosage and duration of treatment vary based on factors such as the size and number of gallstones. While UDCA can be effective for some individuals with cholesterol gallstones, it may not work for everyone, particularly those with larger or calcified stones. It's essential to consult with a healthcare professional to determine the most appropriate treatment approach for gallstones, which may include UDCA therapy or surgical removal of the gallbladder.

Keywords: Ursodeoxycholic Acid, Gallbladder Stone, UDCA, Surgery, Drug, Bladder, Stone.

Introduction

Ursodeoxycholic acid known as ursodiol (USAN) and the abbreviation UDCA, from the root-word for bear urso, as bear bile contains the substance, is one of the secondary bile acids, which are metabolic byproducts of intestinal bacteria. The use of ursodeoxycholic acid (UDCA), also known as ursodiol, in treating liver disease dates back more than a hundred years, when it was first employed in traditional Chinese medicine by herbalists and physicians alike. Before discovering its effectiveness in dissolving gallstones, its primary use was as a liver tonic A well-recognized therapy for biliary disorders such gallstones are Urso-deoxycholic acid (UDCA). The UDCA's mechanisms of action are still not fully understood. For patients with a functional gall bladder, UDCA tablets are approved for the breakdown of small to medium-sized radiolucent gallstones that are high in cholesterol. [1]

A bile acid called ursodeoxycholic acid (UDCA) can aid in the dissolution of some gallstones, particularly those composed mainly of cholesterol. The most prevalent kind of gallstones are cholesterol ones, which develop from an imbalance in bile's constituent parts that causes cholesterol to crystallize. A hydrophilic bile acid known as ursodeoxycholic acid (UDCA; 3, 7-dihydroxy-5-cholanic acid) is being used more and more to treat a range of cholestatic conditions. Though in very small amounts roughly 3.5% of the total bile—it is typically found in human bile. UDCA is used to treat a variety of biliary conditions, including primary biliary cirrhosis, cholestasis in patients receiving parenteral nourishment, and bile duct stones. UDCA is used in the prophylaxis of gallstones during rapid weight reduction. [1]

The two main outcome measures are liver transplantation mortality and mortality. While UDCA treatment reduced ascites, jaundice, and liver biochemistry, it had no effect on liver transplantation or death. The sole FDA-approved medication for PBC is UDCA, which should be taken daily at a dose of 13–15 mg/kg. PBC patients respond to this medication in as much as 67% of cases. In individuals with a functional gall bladder, UDCA tablets are primarily approved for the treatment of primary biliary cirrhosis (PBC) and for the dissolution of small to medium-sized radiolucent, cholesterol-rich gallstones. [2]

Pharmacology of UDCA

Urso-deoxycholic acid (UDCA) is a derivative of cheno-deoxycholic acid. Conversion of chenodeoxycholic acid into ursodeoxycholic acid occurs in two stages via 7- ketolithocholic acid. UDCA acid is a tertiary bile acid that is formed in the liver and a secondary bile acid that is produced in the intestine. [3] Approximately 30 to 60% of UDCA taken orally is absorbed, indicating a good oral bioavailability of the drug. Unconjugated UDCA acid is absorbed via non-ionic passive diffusion8

along the entire length of the jejunum and ileum, while being poorly water soluble in its protonated state. Approximately 20% of the acid may also be absorbed in the colon. Prior solubilization by other bile acids facilitates the absorption of free UDCA. Therefore, it is recommended that UDCA acid be taken with a meal that causes the gallbladder to contract. [3]

Giving UDCA as a taurine conjugate that is soluble in water can help improve absorption. UDCA absorption is hampered by binding substances such cholestyramine, charcoal, and antacids. Following an oral dosage, the high first-pass metabolism (70%) leads to low blood levels of UDCA. In humans, the half-life of UDCA ranges from 3.6 to 5.8 days. UDCA may function through a number of poorly understood processes. The most noticeable change is a decrease in the amount of hydrophobic, poisonous bile acids. The main way that UDCA causes bile desaturation is by reducing the amount of cholesterol secreted into the bile. In addition to suppressing liver cholesterol synthesis and reducing cholesterol absorption, UDCA does not impede the synthesis of bile acids. [4]

Bile's composition can be changed from supersaturated to unsaturated by UDCA. In addition, ursodiol facilitates the creation of liquid cholesterol crystal complexes, which improve the gallbladder's ability to discharge cholesterol into the colon. According to certain theories, UDCA's hydrophilic properties provide cytoprotection in liver necroinflammatory disorders. Some recent research supports its effects on the cell membrane and cellular signal transmission, even if the method by which this is accomplished is still poorly understood. [5]

Mechanism of action

When a patient chooses not to have surgery, the medication dissolves (cholesterol) gallstones by decreasing the absorption of cholesterol. Gallstones likely to return if the patient stops taking the medication and the underlying ailment that caused them does not improve. For these reasons, cholecystectomy surgery has not been replaced by it. Used in conjunction with Naltrexone to alleviate itching in cases of intrahepatic cholestasis in pregnancy. In general, UDCA dissolves cholesterol gallstones over time by reducing the liver's synthesis of cholesterol and raising the amount of bile acids in the bile. Those with tiny, non-calcified cholesterol gallstones and those who have a high risk of gallstone recurrence following surgery are the usual candidates for it. [6]

Role of Ursodeoxycholic Acid (UDCA) In Gall Stones

It has been demonstrated time and time again that cheno-deoxycholic acid (CDCA) is a highly effective dissolving agent for cholesterol gallstones (Barbara et al 1976, Danzinger et al 1972, Gerolami et al 1977, Thistle & Hofmann 1973). Although smaller dosages of the bile acid are occasionally beneficial (of CDCA has also been demonstrated to dissolve cholesterol gallstones), the highest dissolving rate is observed with roughly 15 mg/kg/day (Iser et al 1975, Thistle et al 1978a). The cholesterol saturation index of the bile and the UDCA dose showed a substantial inverse association, according to Maton et al. (1977), although the dose-effect relationship for gallston dissolution is still unclear. To learn more about the dose-effect relationship for the UDCA gallstone dissolving by guest on March 14, 2016 [7]

Cholesterol gallstone disease is a common clinical condition influenced by genetic factors, increasing age, female gender and metabolic factors. Laparoscopic cholecystectomy is currently considered the gold standard in treating patients with symptomatic gallstones. 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. UDCA is indicated in chemo dissolution of bile duct stone. [8]

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. 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. The so-called ternary phase diagram is used to explain the molecular effects of UDCA on bile composition and cholesterol solubility.[9]

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. 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. [9]

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. UDCA therefore could be viewed as the medical treatment of choice for dissolution of cholesterol gallstones. 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. In general, clinical symptoms with gallstone disease are reduced after 3 months of UDCA treatment. [9,10]

Endogenous effects

Primary bile acids are produced by the liver and stored in the gall bladder. When secreted into the intestine, primary bile acids can be metabolized into secondary bile acids by intestinal bacteria. Primary and secondary bile acids help the body digest fats. Ursodeoxycholic acid helps regulate cholesterol by reducing the rate at which the intestine absorbs cholesterol molecules while breaking up micelles containing cholesterol. Because of this property, ursodeoxycholic acid is used to treat (cholesterol) gallstones non-surgically. It is also used to relieve itching in pregnancy for some women who suffer obstetric cholestasis. [11]

While some bile acids are known to be colon tumor promoters (e.g. deoxycholic acid), others such as Urso-deoxycholic acid are thought to be chemo preventive, perhaps by inducing cellular differentiation and/or cellular senescence in colon epithelial cells. It is believed to inhibit apoptosis. Ursodeoxycholic acid has also been shown experimentally to suppress immune response such as immune cell phagocytosis. Prolonged exposure and/or increased quantities of systemic (throughout the body, not just in the digestive system) Ursodeoxycholic acid can be toxic. [11]

Medical uses

Ursodiol is the only FDA approved drug to treat primary biliary cirrhosis. Ursodiol may be used for biliary stasis in pregnant women to relieve the symptoms of itching and decrease bile absorption. In absence of biochemical response to ursodeoxycholic acid in PBC, its use is associated with an incidence of 20% hepatocellular carcinoma in 15 years. In children, ursodeoxycholic acid use is not licensed, as its safety and effectiveness have not been established. Evidence is accumulating that ursodeoxycholic acid is ineffective and unsafe in neonatal hepatitis and neonatal cholestasis. There is insufficient evidence to justify routine use of ursodeoxycholic acid in cystic fibrosis, especially that available data for analysis of long-term outcomes such as death or need for liver transplantation is lacking. Serious adverse events are more common in the ursodeoxycholic acid group than the placebo group. The risk is 2.1 times greater for death, transplantation, or minimal listing criteria in patients on ursodeoxycholic acid than for those on placebo. It is concluded that ursodeoxycholic acid use is associated with improved serum liver tests that do not always correlate with improved liver disease status. [12]

Conclusion & Summary

UDCA therapy usually involves taking oral medication in the form of tablets or capsules. The dosage and duration of treatment can vary depending on factors such as the size and number of gallstones, as well as the individual's overall health. While UDCA can be effective for some people with gallstones, it's not always successful in dissolving stones, particularly larger or calcified ones. Additionally, it may take several months of treatment before any significant changes are observed, and there's a risk of gallstone recurrence once treatment is stopped. It's important for individuals considering UDCA therapy to consult with a healthcare professional to determine if it's the right option for them and to closely follow their provider's guidance throughout treatment. In some cases, surgical removal of the gallbladder (cholecystectomy) may be necessary to effectively manage gallstones and prevent complications.

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