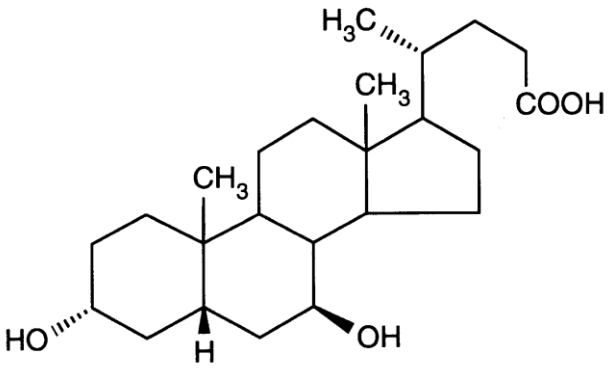
APO-URSODEOXYCHOLIC ACID CAPSULES

NAME OF THE MEDICINE

Ursodeoxycholic Acid (UDCA)

Chemical Name: 3α, 7ß-Dihydroxy-5ß-cholan-24-oic acid

Structural Formula:



Molecular Formula: $C_{24}H_{40}O_4$

Molecular Weight: 394.6 g/mol

CAS Registry Number: 128-13-2

DESCRIPTION

Ursodeoxycholic acid (UDCA) is a white or almost white powder. It is practically insoluble in water, readily soluble in alcohol, sparingly soluble in acetone, in chloroform and in ether. It melts at 200 - 204ºC.

Each capsule contains ursodeoxycholic acid, as the active ingredient. In addition, each capsule contains the following inactive ingredients: maize starch, silicon dioxide and magnesium stearate.
The capsule shell is composed of: titanium dioxide and gelatin.

PHARMACOLOGY

Pharmacological Actions

The mechanism of action of UDCA in liver and cholestatic disorders has not yet been explained totally. However, UDCA alters bile acid composition, resulting in increases in the concentration of UDCA and decreases in the concentrations of the more hydrophobic and potentially toxic bile acids, cholic and chenodeoxycholic acids. UDCA also has a choleretic effect, resulting in increased bile acid output and bile flow. There is some evidence for immunological effects, including a reduction of abnormal expression of HLA Class I antigens on hepatocytes and a suppression of immunoglobulin and cytokine production.

Pharmacokinetics

Absorption

UDCA occurs naturally in the body. After oral administration of a single 500 mg dose of UDCA to healthy volunteers, peak plasma concentrations were 2.7 to 6.3 µg/mL. T_{max} occurs at 60 minutes and a second peak plasma concentration occurs at 180 minutes. After oral administration of 250 mg, 500

mg, 1000 mg and 2000 mg single doses, respective absorption rates were 60.3%, 47.7%, 30.7% and 20.7% based on recovery from bile within 24 hours in patients with external biliary drainage.

Distribution

In plasma, protein binding is 96 – 98%.

First pass extraction of UDCA from the portal vein by the liver ranges from 50 – 70%. UDCA is conjugated to glycine and taurine and then excreted into bile and passes to the small bowel. In the intestine, some conjugates are deconjugated and reabsorbed in the terminal ileum. Conjugates may also be dehydroxylated to lithocholic acid, part of which is absorbed, sulphated by the liver and excreted by the biliary tract. In healthy volunteers given UDCA 500 mg with ^{14}C tracer, 30 – 44% of the dose was excreted in faeces in the first three days as UDCA (2 – 4%), lithocholic acid (37%) and 7-ketolithocholic acid (5%).

Metabolism

The biological half-life, obtained by radioactive labelling, of orally administered UDCA is 3.5 - 5.8 days due to the effective enterohepatic circulation of UDCA in the body.

Excretion

In patients with severe liver disease, renal excretion becomes a major route for elimination of bile acids.

CLINICAL TRIALS

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune disease of the liver marked by the gradual destruction and eventual disappearance of the bile duct epithelial cells. The sustained loss of intralobular bile ducts causes the signs and symptoms of cholestasis, and eventually results in cirrhosis and liver failure. Eight pivotal randomised, controlled studies examined the efficacy of UDCA in the treatment of primary biliary cirrhosis (PBC). All 8 trials were of at least 2 years follow-up. Seven of the eight studies used a dosage in the range of 12 – 16 mg/kg/day; the eighth trial used a significantly lower dose of 7.7 ± 0.2 mg/kg/day. Significant improvement in some or all biochemical tests of liver function was shown in subjects given UDCA during the treatment period. Symptom improvement or improvement in histology were not consistently reported with UDCA but longer survival without liver transplantation was reported in two long term studies. One of the studies reported that the efficacy of UDCA in patients with PBC was greater in patients with less advanced disease (entry bilirubin < 2 mg/dL; histological stage I or II) compared to patients with more advanced disease.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterised by inflammation, fibrosis, and destruction of the large intra- and extrahepatic bile ducts. One pivotal randomised, double-blind placebo-controlled study examines the efficacy of UDCA in the treatment of PSC in 105 patients over 2 years. The dosage used was in the range of 13 – 15 mg/kg/day. Irrespective of initial histological stage, UDCA had no effect on time to treatment failure and survival, without liver transplantation. Serum bilirubin, ALP and AST improved, but UDCA was not associated with a significant improvement in symptoms or histological score.

In three smaller randomised, double-blind, placebo-controlled studies, UDCA similarly showed significant improvement in liver biochemistry (in 2 of the studies) when compared to placebo, but did not significantly improve symptom scores. One study found significant improvement in some liver histological features in the patients treated with UDCA. These trials used UDCA doses ranging from 10 – 15 mg/kg/day.

In a small randomised, double-blind, placebo-controlled study, 20 mg/kg/day UDCA treatment in PSC patients showed improvement in liver biochemistry when compared to placebo. Histological progression was significantly reduced in the UDCA-treated group compared to the placebo-treated group.

Cystic fibrosis-related cholestasis

Cystic fibrosis (CF) is a hereditary disease with multiorgan involvement. Clinical liver disease is rare although many patients may have biochemical evidence of cirrhosis.

One double-blind, placebo-controlled, study randomised 55 patients with CF-related cholestasis to UDCA 900 mg/day or placebo for one year. In addition, taurine supplements or placebo were randomly assigned. Efficacy was assessed by improvements in clinically relevant and nutritional parameters, and liver biochemistry. After one year, the UDCA group had significant improvement in GGT and 5'-nucleosidase but not AST or ALT. However, there was a deterioration of overall clinical condition, as measured by the Shwachman-Kulcycki score in those receiving placebo compared to the UDCA group.

In a dose comparison study, UDCA 20 mg/kg/day for 12 months resulted in a more pronounced improvement in GGT and ALT compared to UDCA 10 mg/kg/day. Improvements in AST and ALP were comparable. Although this study suggested a possible benefit with higher drug doses in resolving liver biochemistry, whether UDCA improves quality of life, histology, or survival is unknown.

INDICATIONS

Ursodeoxycholic acid is indicated in the treatment of chronic cholestatic liver diseases.

CONTRAINDICATIONS

APO-Ursodeoxycholic Acid capsules must not be used if there is hypersensitivity to the active ingredient or any of the excipients.

PRECAUTIONS

During the first three months of therapy, it is advisable to monitor the liver parameters of AST (SGOT), ALT (SGPT), and GGT every 4 weeks, subsequently every 3 months.

Apart from allowing for identification of responders and non-responders in patients being treated for primary biliary cirrhosis, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advance stage primary biliary cirrhosis.

The effect of UDCA in patients with renal impairment has not been studied.

UDCA is not recommended in patients with dominant stenoses of the bile ducts unless the obstructed bile ducts are dilated (see **DOSAGE AND ADMINISTRATION**).

If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued.

Treatment of Patients with Primary Sclerosing Cholangitis

Long periods of high dose UDCA therapy (28-30 mg/kg) in patients with primary sclerosing cholangitis may be associated with a higher rate of serious adverse events

Effects on Fertility

In a fertility study in Sprague-Dawley rats at oral doses up to 2700 mg/kg/day (25 times the maximum recommended human dose of 20mg/kg/day based on body surface area/BSA), no adverse effect on male or female fertility or pregnancy outcome were observed. However, in an oral fertility study in Wistar rats, there was evidence of a reduction in female mating behaviour at doses ≥ 250 mg/kg/day (2 times the maximum recommended human dose based on BSA) and of embryolethality (resulting in a reduction in number of live foetuses) at doses ≥ 1000 mg/kg/day (9 times the maximum recommended human dose based on BSA). Human data on fertility effects following treatment with UDCA are not available.

Use in Pregnancy (Category B3)

UDCA has been shown to cross the placenta in rats. Animal studies have provided evidence of a teratogenic effect of UDCA during the early phase of gestation. In studies in rats, tail malformations occurred after an oral dose of 2000 mg per kg of body weight (18 times the maximum recommended human dose based on body surface area/BSA). In one of two studies in rats, there was evidence of embryolethality, with a reduction in number of live foetuses and live births at oral doses of 2000

mg/kg/day. In studies in rabbits, embryotoxic effects from an oral dose of 100 mg per kg of body weight were found (2 times the maximum recommended human dose). No teratogenic effects were found in the study of UDCA following oral administration to mice or rabbits at doses of up to 1500 and 300 mg/kg/day, respectively (at least 5 times the maximum recommended human dose).

There are no adequate or well-controlled studies in pregnant women during the first trimester. Therefore, UDCA should not be used during the first three months of pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with UDCA.

In women with Intrahepatic Cholestasis of Pregnancy (ICP) UDCA reduces pruritus when given in the second or third trimesters of pregnancy. Data are insufficient to determine the effect of UDCA on neonatal outcomes.

Use in Lactation

It is not known whether UDCA is excreted in human milk, but small amounts of UDCA or its metabolites were excreted in milk of lactating rats following oral administration of 30 mg/kg. In an oral peri-postnatal study in rats, there was a slight transient reduction in postnatal body weight gain of pups at 2000 mg/kg/day (18 times the maximum recommended human dose based on body surface area/BSA).

According to few documented cases of breast feeding women, UDCA was excreted in the breast milk of lactating mothers. The possibility of adverse reactions on the infant should be considered if UDCA is administered to a nursing mother. Alternatively, breastfeeding can be discontinued.

Genotoxicity

UDCA was not genotoxic in the following studies: gene mutation assays (*in vitro* Ames test, gene mutation assay at the TK locus in mouse lymphoma L5178Y cells), assays of chromosome aberrations (analysis of chromosome aberrations in Chinese hamster bone marrow and in spermatogonia of mice, and micronucleus test in hamsters) and assay of sister chromatid exchanges in cultured human lymphocytes.

Carcinogenicity

In two 24-month oral carcinogenicity studies in mice, UDCA at doses up to 1000 mg/kg/day was not tumourigenic. Based on body surface area (BSA), this dose represents 4 times the recommended maximum clinical dose of 20 mg/kg/day. In two 2-year oral carcinogenicity studies in rats, UDCA at doses up to 300 mg/kg/day (3 times the recommended maximum human dose based on BSA) was not tumourigenic.

In 103-week oral carcinogenicity studies of lithocholic acid, a metabolite of UDCA, doses up to 250 mg/kg/day in mice and 500 mg/kg/day in rats did not produce any tumours.

INTERACTIONS WITH OTHER MEDICINES

Some drugs, such as cholestyramine, charcoal, colestipol and certain antacids (containing aluminium hydroxide and/or smectite [aluminium oxide]) bind to UDCA in the intestine and thereby inhibit its absorption and efficacy. Should the use of a preparation containing one of these substances be necessary, it must be taken at least 2 hours before or after UDCA.

UDCA may affect the absorption of cyclosporin in transplantation and nontransplant patients. Therefore, monitoring cyclosporin plasma concentrations are recommended and cyclosporin dose adjusted if necessary.

UDCA has been reported to decrease the absorption of ciprofloxacin in a few cases.

In a clinical study in 12 healthy volunteers with the OATP1B1*1b/*1b genotype, predicting high OATP1B1 activity, it was demonstrated that concomitant use of UDCA (500mg/day) and rosuvastatin (20mg/day) resulted in a significant increase in the plasma levels of rosuvastatin. UDCA increased the AUC of rosuvastatin by approximately 60%, from 145.5 ng/mL per hour to 231.9 ng/mL per hour (p=0.004). Administration of UDCA for 14 days also significantly increased total bilirubin by 139 ± 39% (p=0.003), conjugated bilirubin by 127 ± 29% (p=0.005) and unconjugated bilirubin by 151 ± 52%

(p=0.004). The proposed biological mechanism for this interaction is that bilirubin and rosuvastatin are both metabolites of organic anion transporting polypeptide 1B1 (OATP1B1). OATP1B1 expression is regulated by transcription factor hepatic nuclear factor (HNF) 1α. UDCA acts as an inhibitor of HNF 1α and consequently may decreased expression of OAT1B1. A dose reduction in rosuvastatin should be considered in any individuals exposed to both rosuvastatin and UDCA. The clinical relevance of this interaction with regard to other statins is unknown. However, it is biologically possible that this interaction may also occur between UDCA and other statins which are known substrates of OAT1B1, such as atorvastatin, fluvastatin, simvastatin acid, pitavastatin and pravastatin.

UDCA reduces the peak plasma concentrations (C_{max}) and the area under the curve (AUC) of the calcium channel blocker, nitrendipine. On the basis of this, together with a single case report of an interaction with the substance dapsone (reduction of the therapeutic effect) and *in vitro* findings, it may be assumed that UDCA induces the medicinal product-metabolising enzyme cytochrome P450 3A4. Caution should therefore be exercised in cases of co-administration of medicinal products metabolised by this enzyme, and a dose adjustment may be necessary. Induction has, however, not been observed in a well-designed interaction study with budesonide which is a known cytochrome P450 3A substrate.

ADVERSE EFFECTS

UDCA is generally well tolerated with few side effects. Diarrhoea is the main reported side effect. The incidence of diarrhoea in controlled studies was up to 3%.

Some patients may experience increased pruritus in the early weeks of treatment. In such cases a dose reduction, and thereafter a slow (weekly) increase of dose to the recommended dose, may help.

Severe right upper abdominal pain has occurred during the treatment of PBC (≤1 in 10,000 patients). During advanced stages of PBC, in very rare cases (≤1 in 10,000 patients), decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

Calcification of gallstones can occur in ≤1 in 10,000 patients.

Allergic reactions have been reported in some patients. Urticaria can occur in ≤1 in 10,000 patients).

Other adverse reactions reported include increased cholestasis, nausea, vomiting and sleep disturbance.

DOSAGE AND ADMINISTRATION

Dosage for adults and the elderly:

For PBC and chronic cholestatic liver diseases other than CF and PSC, the dosage of 12 – 16 mg/kg body weight/day of UDCA is recommended.

For CF-related cholestasis, the recommended dose is 20 mg/kg/day of UDCA.

For PSC, the dosage of 10-15 mg/kg body weight/day of UDCA is recommended. A dosage of 20 mg/kg body weight /day has also been shown to improve histology and liver function tests in PSC patients.

Dosage for children:

Data on use in children are very limited. In the few available studies, dosages used have generally been up to 15 - 20 mg/kg/day.

Administration:

For PBC patients: In the first 3 months of treatment, APO-Ursodeoxycholic Acid capsules should be taken in 2 to 3 doses over the day. With improvement of the liver function parameters, the daily dose may be taken as a single dose in the evening.

For other cholestatic liver diseases, APO-Ursodeoxycholic Acid capsules should be taken in 2 to 3 doses over the day.

For patients under 34 kg or patients who are unable to swallow APO-Ursodeoxycholic Acid capsules, UDCA oral suspension should be used (available from other brands).

The capsules should be swallowed whole with some liquid.

Care should be taken to ensure that UDCA is taken regularly.

In patients with PBC, there may, in rare cases, be an initial deterioration in symptoms, e.g. itching. If this is the case, therapy can be continued with 1 capsule of UDCA daily, and the daily dose gradually increased weekly until the recommended daily dose has been reached.

For PSC patients, dominant stenoses of the bile ducts should be dilated before and during treatment with UDCA.

OVERDOSAGE

Symptoms

Diarrhoea may occur in cases of overdosage. If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued. No specific counter-measures are necessary and the consequence of diarrhoea should be treated symptomatically with restoration of fluid and electrolyte balance.

In general, other symptoms of overdosage are unlikely because the absorption of UDCA decreases with increasing dose and therefore more is excreted with the faeces.

Treatment

Serious adverse effects are also unlikely to occur in overdosage. However, liver function should be monitored. If necessary, ion-exchange resins may be used to bind bile acids in the intestines.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

APO-Ursodeoxycholic Acid capsules are intended for oral administration. Each capsule contains 250 mg of Ursodeoxycholic Acid, as the active ingredient.

APO-Ursodeoxycholic Acid capsules 250 mg:

White hard gelatine capsules. The content – white or almost white powder

Blister Pack (Clear PVC/Aluminium silver foil) of 100 capsules (AUST R 276339).

Storage

Below 25^0C.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 20 APRIL 2017