# PHARMACOLOGY OF URSODEOXYCHOLIC ACID


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**According to prof. Omnia the exam is from the blue slides only**

**Important notes are underlined**

**Good Luck ^_^**

# URSODEOXYCHOLIC ACID (UDCA)

A naturally occurring, endogenous, hydrophylic secondary bile acid.

It is a metabolic by product of intestinal bacteria formed in caecum. Little is found in humans/ high concentrations are found in black bears found in a little small amount because its reabsorped and recycled

[NOT IMPORTANT] When pure it comes as white or almost white, crystalline powder, practically soluble in water, freely soluble in alcohol, sparingly soluble in chloroform.

## Pharmacokinetics:

- It is absorbed from the GIT and undergoes enterohepatic recycling.
- It is partly conjugated in the liver before being excreted into the bile.
- Little is influenced by intestinal bacterial degradation i.e little converts to lithocholic acid which mostly excretes in faeces.

If traces are reabsorbed it conjugates, gets sulphated in liver before excretion. That is one of the reasons why it is much safe than other bile a. preparations.

For understanding :

### 1-GALLSTONES :

They are caused by combination of

Poor liver function → altering composition ratios →supersaturation of bile constituents by (Hypersecretion of cholesterol + Hyposecretion of bile salts) → bile stasis in presence of nucleation factors such as mucin, GPs, Ca. → trap of cholesterol crystals → precipitate

Incomplete gallbladder contractions (Infections, inflammations, stagnation)

### 2- CHOLESTATIC LIVER DISEASE :

When concentrations of bile acids become high intracellularly or extracellularly → they exert toxicity to cells.

Their cytotoxicity is involved in the pathogenesis of several liver, biliary & intestinal diseases and colon cancer..

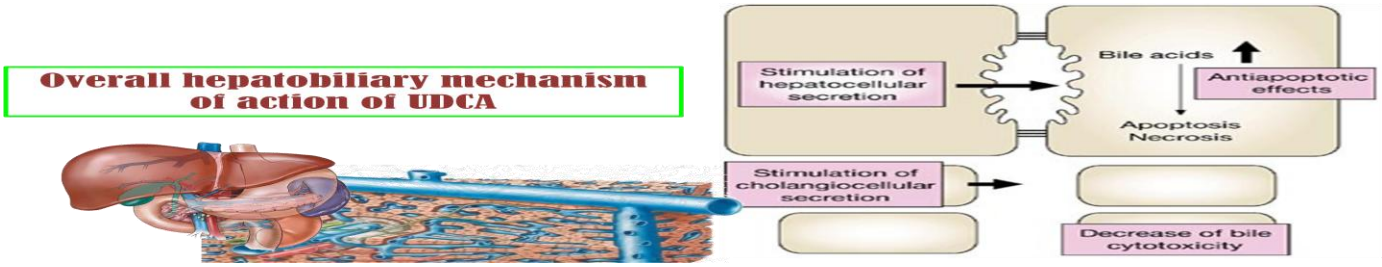
Cytotoxicity is strongly related to their structure: the greater the hydrophobicity (lipophylicity), the greater the cytotoxicity

### 3- CYSTIC FIBROSIS : is a common recessive genetic disease

# the Mechanisms are very important #

## Pharmacodynamics :

| Mechanisms that prevent formation or enhance dissolution of GALLSTONES | Mechanisms that are cytoprotective in cholistatic liver disease | Mechanisms acting against hepatic complications of cystic fibrosis |
|---|---|---|
| **Choleretic effect : Stimulation of hepatobiliary secretion**<br>❖ It enhances conversion of cholesterol to bile acids → ↓ biliary output of cholesterol (approximately 50%).<br>❖ Fasting duodenal (gallbladder) bile becomes desaturated → prevents crystals formation. This allows gradual extraction of cholesterol from existing stones<br>❖ It competes with lipophilic (hydropobic) bile acids in small intestine → ↓ their absorption → ↓ their plasma concentrations, their pool sizes, their fractional turnover rates → This contributes to stimulation of hepatobiliary secretion<br>❖ It inhibits intestinal absorption of cholestrol<br>**Conclusion :**<br>- It attacks the cholesterol & decreases it.<br>- it increases the fluidity and secretion . | Cholestasis is characterized by hepatocellular &/or cholangiocytic bile-acid retention &/or injury.<br>UDCA renders bile more hydrophilic, so exerts cytoprotective effects;:<br>(1) detoxification of the cytoxic hydrophobic bile acids<br>detoxification : treatment for poisoning by neutralizing the toxic properties<br>(2) protection of injured cholangiocytes against toxic effects of bile a.<br>(3) inhibition of apoptosis of hepatocytes.<br>(4) stimulation of impaired hepatobiliary secretion<br>On molecular level; UDCA conjugates may improve impaired secretory capacity of the cholestatic liver by modulating complex intracellular signaling cascades including calcium, PKC, MAP kinases, and transcription factors that will promote expression of transporter proteins, exert antioxidant effects & inhibit apoptosis by modulation of the mitochondrial death pathways | In cystic fibrosis; UDCA → stimulation of cholangiocellular calcium-dependent secretion of chloride & bicarbonate ions .i.e. activation of a $Ca^{++}$-dependent Cl channel & concomitant stimulation of $Cl/HCO_3$ secretion. |




# PRINCIPLES OF BILE ACID THERAPY:

## 1. As displacement therapy

**The demand is to alter the composition of the circulating bile acids with objective of:**

- **Decreasing the cytotoxiciy of accumulated endogenous bile acids**
- **Modulating cholesterol metabolism, saturation & secretion → ↓ cholestrol content , ↓ biliary deposition & crystaliation**
- **→ *policy for prevention or treatment of stones***

## 2. As replacement therapy

**To correct bile acid deficiency & its consequence of mal absorption, fat soluble vitamin deficiency,...**

# Clinical Uses of UDCA :

- **Inborn errors of bile acid biosynthesis Given with other bile acid.** } **REPLACEMENT**

- **Dissolution of cholesterol stones**
- **Prevention of formation of cholesterol stones**
- **Cytoprotection in Cholistatic liver diseases**
- **Improvement of Hepatic component of cystic fibrosis**

} **DISPLACEM**

# Clinical Uses : ((DISPLACEM ))

## DISSOLUTION OF CHOLESTEROL STONES

- Only in those patients with a high operative risk or do not want surgery
- Only for cholesterol stones better < 1 cm in diameter
- It is ineffective for the dissolution of calcified & pigment gall stones
- Of no value in patients without a patent functioning gall bladder
- Given for at least 1 to 2 years in most patients.
- Success & progress of therapy is monitored by using ultrasound
- Recurrence rate within 5 years is high after cessation of therapy [30% – 50%]

## *PREVENTION* OF FORMATION OF CHOLESTEROL STONES <<imp

Cholesterol stones can form in 20-30% of patients who are on very low-caloric diets and losing weight very quickly or in 30-40% of who underwent gastric bypass 30-40% ➔ develop cholesterol stones.

- So dieticians recommend UDCA for prophylaxis in rapid weight loss and surgeons recommend removal of the gallbladder prophylactically at the time of surgery !!!
- In patient on total parenteral nutrition-which results in gallbladder stasis & distension , it is also recommend to give UDCA for prophylaxis

## CYTOPROTECTION IN *CHOLESTATIC LIVER DISEASES* <<imp

- In early-stage of primary biliary cirrhosis and primary sclerosing cholangitis, protection of injured cholangiocytes against the toxic effects of bile acids might prevail, while stimulation of impaired hepatocellular secretion and inhibition of bile-acid-induced hepatocyte apoptosis seems to be relevant in more advanced cholestasis
- In intrahepatic cholestasis of pregnancy and drug induced-cholestasis, stimulation of impaired hepatocellular secretion could be crucial for rapid relief of symptoms helped by adjuvance of cholystyramine to control severe pruritus (an intense itching sensation that can have various causes as by allergies or infection .. etc) ➔ TAKE CARE of INTERACTIONS

## CYTOPROTECTION HEPATIC INJURY IN *CYSTIC FIBROSIS* <<imp

- In cystic fibrosis, stimulation of cholangiocellular calcium-dependent secretion of chloride & bicarbonate could have major impact on inhibition of bile-acid-induced hepatocyte apoptosis caused by hepatocellular bile-acid retention

## ADRS :

1. GIT; abdominal cramping, diarrhea, constipation, gas, nausea, lack of appetite, peptic ulcer
2. Skin; dry skin or excessive sweating and thinning of hair paradoxical worsening of pruritus which responds to cholestyramine
3. Allergic Response to bile salts; range form mild as generalized itching, rash, to severe reactions as respiratory distress
4. Nervous System; headache, tiredness, generalized weakness, depression, anxiety & difficulty sleeping
5. Others ↓ white blood cell count, ↑ glucose, LDL & creatinine levels

## Contraindications :

1. In patients with chronic liver disease.
2. Peptic ulcer
3. Inflammatory bowel disorders
4. In pregnancy

## Interactions :

1. Cholystyramine; reduces the effectiveness of UDCA. Unfortunately the two drugs must be taken together in most cholistatic hepatic disorders to cure the existing pruritus The only way is to space them 4 hours apart in dosing.
2. With any other bile a. binding drugs as some antacids, charcol, sequestrantes & resins (used in hypercholestrolemia),,….
3. With drugs which increase cholesterol elimination in bile, e.g. estrogenic hormones, contraceptive pills, fibrates
4. UDCA increases absorption of cyclosporine