Ursodeoxycholic Acid
Newborn use only

2024

Alert	Hyperosmolar suspension. In-house suspension has an osmolality of 1030 mOsm/kg.[15]
Indication	Treatment of neonatal cholestasis Pretreatment for hepatobiliary scintigraphy (DISIDA or HIDA scan) Adjuvant therapy for unconjugated hyperbilirubinemia has been reported
Action	Naturally occurring **hydrophilic** bile acid. Oral administration increases hydrophilic bile acid, replacing/displacing toxic concentrations of endogenous hydrophobic bile acids that tend to accumulate in cholestasis. Other actions include protection of the injured bile duct epithelial cells (cholangiocytes) against toxic effects of bile acids, inhibition of apoptosis of hepatocytes, immunomodulatory effects, and stimulation of bile secretion by hepatocytes and cholangiocytes.[8,9]
Drug type	Bile acid
Trade name	Ursofalk Suspension [Dr Falk Pharma][8] or suspension compounded by local pharmacy
Presentation	50 mg/mL oral suspension
Dose	**Neonatal cholestasis** 10-15 mg/kg/dose 12 hourly[1-5] **Pretreatment for hepatobiliary scintigraphy (DISIDA or HIDA scan)** 10 mg/kg/dose 12 hourly for 48-72 hrs prior to scan and continue until scan is over.[16] **Adjuvant to phototherapy in term neonates has been reported.** 5 mg/kg/dose 12 hourly (until phototherapy is ceased)[10-14]
Dose adjustment	No information.
Maximum daily dose	30 mg/kg
Total cumulative dose	
Route	Oral/intragastric
Preparation	Not applicable
Administration	Administer mixed with 1-2 mL of milk/sterile water into infant's mouth through a feeding teat or via intragastric tube.
Monitoring	Liver function and total and direct serum bilirubin. Observe stool colour.
Contraindications	Hypersensitivity to ursodeoxycholic acid. Complete biliary obstruction.
Precautions	
Drug interactions	Antacids which contain aluminium bind to ursodeoxycholic acid and reduce its absorption.
Adverse reactions	NOTE: Hyperosmolar suspension. In-house suspension has an osmolality of 1030 mOsm/kg.[15] Adult data[9] Dermatologic: Rash Gastrointestinal: Constipation, diarrhoea, indigestion, vomiting Musculoskeletal pain Respiratory: Bronchitis, cough, pharyngitis, upper respiratory infection Immunologic: Hypersensitivity reaction
Compatibility	Not applicable
Incompatibility	Not applicable
Stability	Discard 4 months after opening.
Storage	Store below 25°C.
Excipients	Ursofalk suspension: benzoic acid, purified water, xylitol, glycerol, Avicel RC-591, propylene glycol, sodium citrate dihydrate, sodium cyclamate, citric acid, sodium chloride and 87017 lemon flavour
Special comments	
Evidence	**Efficacy** **Treatment of parenteral nutrition associated cholestasis (PNAC):** A cross-over randomised controlled trial compared the effectiveness of phenobarbital versus ursodeoxycholic acid (UDCA) in

reducing the direct serum bilirubin levels in preterm neonates with PNAC. Infants randomly received one of the two interventions: UDCA (10 mg/kg/day every 12 hours) or phenobarbital (3 mg/kg/day, every 24 h) for 7 days, continuing with 7 days of wash-out to return to their initial state and to subsequently receive the other treatment. UDCA therapy resulted in decrease in serum bilirubin. Phenobarbital had no effect in reducing bilirubin concentration.[1] A few retrospective studies reported the effect of UDCA in very-low-birth-weight (VLBW) infants with PNAC. Chen et al reported significantly shorter duration of cholestasis and lower peak bilirubin levels with UDCA dosages of 10-30 mg/kg/day.[2] Thibault et al reported significantly faster rate of decline in bilirubin and significant weight gain with UDCA. The median (interquartile range) dose and duration of UDCA therapy were 25 (20-29.4) mg/kg/day and 35 (22-64) days.[3] Al-Hathlol et al reported improvement in liver function tests with UDCA of 15-20 mg/kg/day in a small cohort of preterm infants with intractable PNAC. There was a significant reduction in serum levels of direct bilirubin, total bilirubin and AST. Serum ALP, ALT and GGT showed a non-significant improvement. Serum direct bilirubin was noted as the first marker to respond to UDCA therapy.[4]

Treatment of neonatal cholestasis from diverse etiologies: Lewis et al compared the effectiveness of ursodiol and phenobarbital for the treatment of cholestasis in neonates. UDCA was significantly more effective in reducing direct bilirubin than phenobarbital. Phenobarbital, has limited efficacy for the reduction of direct bilirubin in infants with cholestasis. There was no improvement in direct bilirubin in the majority of infants treated with phenobarbital.[5]

Prevention of PNAC: A pilot trial by Arsanoglu et al administered UDCA 5 mg/kg/day beginning on day 3 of life in very preterm infants on PN from day 1 of life. The dose was increased to 10 mg/kg/day with initiation of enteral feeds and dose was further increased to 20 mg/kg/day once enteral feeds reached 120 mL/kg/day. Primary aim was to reduce fecal fat excretion and time to reach full enteral feeds. Secondary outcomes included liver enzymes. UDCA treatment showed no significant benefit in fecal fat excretion and time to reach full enteral feeds. However, Y -glutamyl transferase (GGT), the earliest sensitive marker for cholestasis, declined significantly in UDCA treated infants.[6] A double blind, randomized, controlled trial in which three groups of preterm infants (birth weight <1500 g) were randomized to erythromycin (12.5 mg/kg/day), UDCA (5 mg/kg every 6 h) or placebo treatment. Time to achieve full feeding was significantly shorter in the erythromycin group. GGT level was slightly lower in UDCA groups than erythromycin. The maximum serum total bilirubin and conjugated bilirubin levels, serum alanine aminotransferase and aspartate aminotransferase levels did not differ significantly among three groups. This trial suggested that prophylactic usage of UDCA could be considered in infants with prolonged parenteral nutrition.[7]

Hepatobiliary scintigraphy – commonly referred to DISIDA (Diisopropyliminodiacetic acid) and HIDA (Hepatobiliary iminodiacetic acid) scans: UDCA is significantly more effective in neonatal cholestasis than phenobarbital.[5] Society of Nuclear Medicine (SNM) practice guidelines recommend pretreatment with UDCA prior to test. The dose is 20 mg/kg/day in 2 divided doses (12 hours apart) for 2–3 days before the scan and continued until the test is over. In comparison to phenobarbital, UDCA does not cause sedation in infants and may be an advantage in certain patients. Another advantage to consider is shorter premedication. Alternative to UDCA is pretreatment with 3-5 day course of 5 mg/kg/day of phenobarbital.[16]

Adjuvant therapy for unconjugated hyperbilirubinemia: Several RCTs demonstrated faster decline in total serum bilirubin when UDCA was given in addition to phototherapy in term neonates. Hassan et al enrolled 200 term neonates with indirect hyperbilirubinemia under phototherapy and randomly divided into two groups, group A (n=100) received Ursodiol 10 mg/kg/day orally divided 12 hourly after day 3 of life in addition to phototherapy, while group B (n=100) received only phototherapy. Total serum bilirubin at 12, 24 and 36 hours after therapy were significantly less in UDCA group and the duration of phototherapy was also significantly less.[10] In a double blind RCT, Honar et al enrolled 80 term neonates >3 days old under phototherapy and randomly divided into 2 groups. The intervention group received UDCA 10 mg/kg/day divided every 12 hours in addition to phototherapy, whereas the control group (n=40) received only phototherapy. Total serum bilirubin levels at 12, 24 and 48 hours after the beginning of therapy were significantly less and duration of phototherapy was significantly less in UDCA group.[11] Jafari et al randomised 96 term neonates from 24 hours to 14 days of age under phototherapy into 3 Groups receiving either phototherapy only or UDCA at

	10mg/kg/day or 20mg/kg/day in 12 hourly doses along with phototherapy. There was a higher rate of fall in serum bilirubin and less duration of phototherapy required in children receiving UDCA. However, there was no difference in the group receiving 10mg vs 20 mg /kg/day.[12] In a double blind RCT by Shahramian et al, term neonates of 3-5 days age under phototherapy were randomly divided into intervention (phototherapy+ UDCA) and control (phototherapy alone) groups. The intervention group received 15 mg/kg UDCA daily. Total serum bilirubin levels at 24, 48 and 72 hours after therapy were significantly less in UDCA group. The ratio of neonates with total bilirubin< 10 mg/dL were 28% and 55% after 48 hours, and 64% and 90% after 72 hours of therapy initiation in phototherapy alone and phototherapy+ UDCA groups respectively (P< 0.001). The mean reduction of direct bilirubin was not significantly different between the groups.[13] In a RCT by Akefi et al, 220 term neonates receiving phototherapy for non-haemolytic jaundice were randomly assigned to phototherapy group (Control group) and phototherapy plus UDCA group (Intervention group) as 10mg/kg/day in 2 divided doses. The mean age of the control and intervention group was 5.3 and 4.9 days, respectively. Reduction in total bilirubin level was significantly more in UDCA group. However, there was no significant difference in mean of the duration of phototherapy.[14] **Safety** UDCA is well tolerated with no significant adverse effects reported in neonatal studies.[1-7]
Practice points	UDCA is effective in reducing direct serum bilirubin and duration of PNAC in neonates. (LOE III-2; GOR B)[1-5] Prophylactic usage of UDCA can be considered in infants with prolonged PN. (LOE III-2; GOR D)[6,7] UDCA may be considered as an additive therapy to phototherapy in term neonates with indirect hyperbilirunemia to facilitate faster decline in total serum bilirubin. (LOE II: GOR C)[10-14]
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