Ursodeoxycholic Acid
Newborn use only

2021

Alert	
Indication	Cholestasis
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 apotosis 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	20-30 mg/kg/day in 2-3 divided doses (1-5)
Dose adjustment	No information.
Maximum daily dose	30 mg/kg
Total cumulative dose	
Route	Oral
Preparation	Not applicable
Administration	Oral or intragastric. Administer undiluted or mixed with a small amount of milk into infant's mouth through a feeding teat or via intragastric tube.
Monitoring	Liver function and 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	Adult data (9) Dermatologic: Rash Gastrointestinal: Constipation, diarrhea, 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:** There are no prospective studies evaluating the use of UDCA with the primary objective of clinical 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) **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)
References	1. Maldonado SR, Téllez NCG, Yescas-Buendía G, FernanCarrocera L, Echaniz-Aviles O, Ríos ERR. Effectiveness of ursodeoxycholic acid vs phenobarbital for the treatment of neonatal cholestasis: a cross-randomized clinical trial. Bol Med Hosp Infant Mex. 2010;67:418-23. 2. Chen C-Y, Tsao P-N, Chen H-L, Chou H-C, Hsieh W-S, Chang M-H. Ursodeoxycholic acid (UDCA) therapy in very-low-birth-weight infants with parenteral nutrition-associated cholestasis. The Journal of Pediatrics. 2004;145(3):317-21. 3. Thibault M, McMahon J, Faubert G, Charbonneau J, Malo J, Ferreira E, et al. Parenteral nutrition-associated liver disease: a retrospective study of ursodeoxycholic Acid use in neonates. The Journal of Pediatric Pharmacology and Therapeutics. 2014;19(1):42-8. 4. Al-Hathlol K, Al-Madani A, Al-Saif S, Abulaimoun B, Al-Tawil K, El-Demerdash A. Ursodeoxycholic acid therapy for intractable total parenteral nutrition-associated cholestasis in surgical very low birth weight infants. Singapore medical journal. 2006;47(2):147. 5. Lewis T, Kuye S, Sherman A. Ursodeoxycholic acid versus phenobarbital for cholestasis in the Neonatal Intensive Care Unit. BMC pediatrics. 2018;18(1):1-6. 6. Arslanoglu S, Moro GE, Tauschel H-D, Boehm G. Ursodeoxycholic acid treatment in preterm infants: a pilot study for the prevention of cholestasis associated with total parenteral nutrition. Journal of pediatric gastroenterology and nutrition. 2008;46(2):228-31. 7. Gokmen T, Oguz S, Bozdag S, Erdeve O, Uras N, Dilmen U. A controlled trial of erythromycin and UDCA in premature infants during parenteral nutrition in minimizing feeding intolerance and liver function abnormalities. Journal of Perinatology. 2012;32(2):123-8. 8. Product Information: Ursofalk Suspension. MIMSOnline. Accessed on 31 March 2021. 9. Micromedex. Ursodeoxycholic acid. Accessed on 3 April 2021.

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