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Use of Ursodiol in Infants and Children

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Ursodiol was approved by the Food and Drug Administration (FDA) in 1987 for the prevention and treatment of gallstones and for the treatment of primary biliary cirrhosis in adults.¹ Although not approved by the FDA for use in pediatric patients, ursodiol has been used for two decades as adjunctive therapy in the management of children with hepatobiliary disease.² Initially studied in adolescents with cystic fibrosis, ursodiol has also been found to be useful in the management of infants and children with hereditary cholestasis syndromes, biliary atresia, and parenteral nutrition-associated cholestasis. This issue of *Pediatric Pharmacotherapy* will provide an overview of recent studies conducted with ursodiol in infants and children with hepatobiliary diseases, as well as review its mechanism of action, pharmacokinetics, and adverse effects.

Mechanism of Action

Ursodiol (usodeoxycholic acid) is a normal, although minor, component of human bile acids. It inhibits absorption of cholesterol in the intestine and suppresses hepatic synthesis and secretion of endogenous cholesterol. Ursodiol is a hydrophilic bile acid that solubilizes cholesterol and promotes its dispersion in aqueous fluids, reducing viscosity and improving bile flow. As a result, ursodiol reduces cholestasis, as well as prevents formation and promotes dissolution of cholesterol-containing gallstones.¹⁻³

In patients with hepatic disease, ursodiol protects hepatocytes from the cytotoxic effects of hydrophobic bile acids by competitive inhibition of their absorption in the intestine. Administration of exogenous ursodiol increases the percentage of ursodiol in the bile acid pool from 1-2% to 60% with repeated dosing. By altering the content of the normal bile acid pool, ursodiol reduces the intrahepatic concentration of these cytotoxic endogenous bile acids and prevents their accumulation in patients with cholestasis. In addition to preventing direct hepatocyte

damage from mitochondrial dysfunction and free radical generation, the cytoprotective and immunosuppressive effects of ursodiol may decrease the rate of hepatocyte apoptosis and fibrosis, as well as reduce injury to bile ducts and prevent abnormal bile duct proliferation.¹⁻³

Pharmacokinetics

After oral administration, approximately 90% of an ursodiol dose is absorbed in the proximal jejunum and the ileum by passive diffusion. After absorption, it is extracted from the portal vein circulation by the liver. Ursodiol is then conjugated with glycine or taurine and secreted into the bile. Initially concentrated in the gallbladder, conjugated ursodiol passes into the duodenum via the cystic and common ducts. Only small amounts of ursodiol are present in the systemic circulation.¹⁻³

Ursodiol undergoes extensive enterohepatic recirculation and may be oxidized or reduced by bacteria in the gut, producing 7-keto-lithocholic acid and lithocholic acid. These metabolic byproducts are eliminated in the feces. Urinary excretion accounts for only 1% of an oral dose. The elimination half-life of ursodiol in adults is approximately 3 to 6 days. Steady state concentrations are typically reached within 3 weeks of starting therapy. Within a week after discontinuation of therapy, ursodiol concentrations in the bile will have declined to approximately 5 to 10% of the average concentration at steady state.¹⁻⁴

Clinical Trials

Ursodiol has been used as adjunctive therapy in the management of infants and children with hepatic and biliary cholestasis since its introduction onto the U.S. market in 1987. There are now several dozen papers describing its use.² The earliest papers focused on the treatment of adolescents with hepatobiliary disease resulting from cystic fibrosis. In several publications, ursodiol in doses of 10-20 mg/kg/day resulted in improved biochemical markers of cholestasis, as

well as increased fat absorption.^{2,5,6} Ursodiol has also been used successfully in the management of hereditary conditions associated with hyperbilirubinemia and cholestasis, including Crigler-Najjar disease and Kabuki syndrome.^{2,7,8}

Another long-standing use for ursodiol has been as an adjunct in the management of infants and children with biliary atresia. In 1987, Ullrich and colleagues treated two children with biliary atresia who failure to gain weight on maximal nutritional support had reduced their likelihood for successful liver transplantation.⁹ Treatment with ursodiol, at a dose of 17 mg/kg/day given once daily at bedtime, resulted in clinically significant gains in both weight and length. One of the children also showed improvement in their hepatic function.

Since that publication, a number of other papers have further substantiated the benefit of ursodiol in pediatric patients with biliary atresia. Although it does not appear to alter the outcome of the disease, ursodiol may help to retard its progression and improve patient symptoms. In 2007, Stringer and colleagues at St. James's University Hospital published a series of 71 infants treated for biliary atresia.¹⁰ Of the 60 who underwent a Kasai portoenterostomy, 50 received adjunctive therapy with oral dexamethasone for a 15 day period post-operatively, along with a regimen of ursodiol 5 mg/kg twice daily and phenobarbital 5 mg/kg once daily at bedtime for one year. Thirty-eight (76%) of the 50 infants who received the adjunctive therapy cleared their jaundice, defined as having a bilirubin level < 20 micromol/L, compared to only 4 (40%) of the 10 who were not treated (p=0.06). At the end of the study, cholangitis was significantly less common in the adjunctive therapy group compared to those who were not treated (36% versus 80%, p<0.05). Of the 56 children from both groups surviving at the end of one year, 70% had not required liver transplantation at a median follow-up of 3.3 years. Based on their results, the authors concluded that their adjunctive regimen significantly improved clinical outcomes after a Kasai procedure.

These results were confirmed by a prospective study of 16 children with biliary atresia. In 2008, Willot and colleagues found that treatment with ursodiol after Kasai portoenterostomy improved liver function.¹¹ The authors evaluated patients who underwent a Kasai and were treated with ursodiol (mean dose 25 mg/kg/day, range 20-36 mg/kg/day) for at least a year after surgery. The decision to discontinue therapy was made by the attending physician. In 13 of the 16 patients,

biochemical tests demonstrated significant worsening of hepatic function after discontinuation. Alanine aminotransferase (ALT) rose from 1.4 xN (the upper limit of the normal range) to 3.0 xN after discontinuation. Gama glutamyl transpeptidase (GGT) increased from 4.2 xN to 8.0 xN and aspartate aminotransferase (AST) rose from 1.3 xN to 1.7 xN. All of these patients responded to the resumption of therapy with improvement in their biochemical markers as well as a reduction in endogenous bile acid concentrations.

In contrast, Kotb found less favorable results in a review of 141 children who underwent a Kasai portoenterostomy at New Children's Hospital in Cairo between May 1985 and June 2005.¹² A total of 108 children were treated with ursodiol (mean dose 20 mg/kg/day) for an average duration of 252.6±544.9 days. More of the untreated patients were classified as having a successful outcome than the ursodiol-treated patients (8/33 or 24.2% versus 11/108 or 10.4%, p=0.043). There was no significant difference in the number of patients who failed therapy and required additional intervention (75.7% of the treated versus 77.7% of the untreated patients, p=0.489). The incidence of diarrhea was also significantly greater in the treated group (70.4% versus 6%, p=0.0001), leading the authors to conclude that ursodiol offered no significant benefit and could produce unnecessary complications.

Ursodiol has also been used in the treatment of parenteral nutrition-associated cholestasis (PNAC) in infants and children.^{13,14} The incidence of PNAC ranges from 7 to 57%, with the highest percentages occurring in very-low-birthweight infants requiring long-term parenteral nutrition. In 2004, Chen and colleagues reviewed their experience with ursodiol in 30 infants with PNAC (mean gestational age 28±0.44 weeks), including 12 who received ursodiol and 18 untreated patients who served as controls.¹³ Ursodiol was initiated at the time cholestasis was diagnosed and patients were treated with 10 to 30 mg/kg/day, divided into three doses. The average duration of treatment was 51.5±8.5 days. The infants in the ursodiol group had a shorter duration of cholestasis compared to the controls (62.8 versus 92.4 days, p=0.006). Peak total bilirubin was also lower in the treatment group (8.8±1.6 versus 13.9±1.6 mg/dL, p=0.007). There were no significant differences in ALT, GGT, or AST. None of the patients in the study progressed to hepatic failure and there were no mortalities. There were no adverse effects reported with the use of ursodiol.

In 2006, De Marco and colleagues conducted a prospective evaluation of the effects of ursodiol in 12 children with short bowel and PNAC.¹⁴ The patients were treated with an ursodiol dose of 30 mg/kg/day divided and given three times daily. At the 6-month evaluation period, 11 children had full remission or improvement in their cholestasis. The mean time to improvement was 2.1 months (range 1-4 months). Average values of ALT, GGT, and direct bilirubin improved significantly after treatment. Of the four children who were taken off ursodiol at the completion of the study, three had a return of their cholestasis. These three children were placed back on ursodiol with subsequent improvement. The authors reported no serious adverse effects related to treatment.

Based on the success of these investigations as well as others, Arslanoglu and colleagues recently published the results of a pilot study using ursodiol as preventative therapy for PNAC in premature infants.¹⁵ The authors conducted their prospective, double-blind, placebo-controlled trial in 30 infants. Beginning on the third day of life, patients were randomized to receive ursodiol (5 mg/kg/day) or placebo. Once enteral feedings were initiated, the ursodiol dose was increased to 10 mg/kg/day and continued until the last day of parenteral nutrition. At that time, the ursodiol dose was increased to 20 mg/kg/day. There was no significant difference in fat absorption between the groups. Fecal fat excretion was slightly decreased in the ursodiol group, but the difference did not reach statistical significance. The treated group reached full enteral feeds two days earlier than the controls, but there were no differences in growth or nutritional status. Serum GGT levels declined throughout the treatment period in the ursodiol group, while increasing in the controls. Serum AST and ALT declined significantly with ursodiol, while AST increased and ALT remained unchanged in the controls ($p < 0.05$). There were no significant adverse effects associated with ursodiol administration. The authors concluded that the results of their pilot study support the need for additional research with ursodiol as preventative therapy in premature infants at risk for PNAC.

Adverse Effects

Ursodiol is generally well tolerated. In clinical trials of adults, the most frequently reported adverse effects have been nausea (in 14-17% of patients), dyspepsia (16%), diarrhea (25-27%), constipation (9-26%), headache (18-25%), dizziness (16%), and back or abdominal pain (11-43%).^{1,3} In children, the most frequently reported adverse effect has been diarrhea.¹²

Although ursodiol administration has not been associated with the development of hepatic injury during clinical use, there is a potential risk for hepatotoxicity from accumulation of the lithocholic acid metabolite. Lithocholic acid has been found to produce cholestatic injury and liver failure in animal models. This could theoretically occur in humans who lack the ability to form sulfate conjugates. It is recommended that all patients have serum transaminases measured prior to starting therapy and periodically thereafter, guided by the current recommendations for monitoring their underlying hepatic or biliary disease.¹⁻³

A single report of an ursodiol overdose in an infant resulted in no significant adverse effects.¹⁶ The patient was a 39 day old infant, born at 32 weeks, who was being treated with ursodiol for PNAC and hyperbilirubinemia. She was discharged on 20 mg ursodiol (2 mL of a 10 mg/mL compounded suspension) every 8 hours, to give a dose of 25 mg/kg/day. The preparation that the patient received at discharge was a 60 mg/mL suspension. Although the instructions on the label were to give 0.33 mL (20 mg) of this more concentrated suspension, the parents continued to administer 2 mL doses. This resulted in the patient receiving 80 mg every 8 hours (148 mg/kg/day). The error was discovered six days later and the family was sent to an emergency department. The patient appeared to be in no distress, with no history of vomiting or diarrhea. Her serum transaminases were within the normal range (AST 33 U/L and ALT 22 U/L) and serum bilirubin was 1.6 mg/dL. She was discharged without further intervention. While this case report demonstrates the relative safety of ursodiol, it also highlights the need for caution when using extemporaneous (compounded) formulations.

Drug Interactions

Antacids and bile acid sequestrants (colestipol and cholestyramine) may reduce the absorption of ursodiol and reduce its efficacy. Drugs that increase cholesterol secretion, such as clofibrate, estrogens, and oral contraceptives, may counteract the effects of ursodiol. Concomitant administration of these agents may blunt the efficacy of ursodiol in preventing gallstone formation. Lipid-lowering agents, such as HMG-CoA reductase inhibitors, may also counteract the effects of ursodiol, but these interactions have not been well studied.^{1,3}

Dosing Recommendations

The recommended dose of ursodiol for infants and children, based on clinical trials and case series, is 5 to 30 mg/kg/day, given in two or three

divided doses.^{2,5-15} In adults, the recommended dose is 300 mg given twice daily. For patient with primary biliary cirrhosis, the recommended dose is 13 to 15 mg/kg/day divided in 2 to 4 doses per day.^{1,3}

Availability

Ursodiol is marketed as Actigall® (Watson) and as a generic product in 300 mg capsules. It is also available from Axcan Pharma in 250 mg tablets (URSO 250®) and 500 mg tablets (URSO Forte®).^{1,3} Several extemporaneous formulations for oral suspensions have been published, with ursodiol concentrations ranging from 10 to 60 mg/mL.¹⁷⁻¹⁹ As described previously, it is essential that all care providers, including family members, be aware of the need to check the suspension concentration to ensure that the correct dose is being administered.

Summary

Ursodiol has proven to be a useful tool in the management of infants and children with hepatic and biliary dysfunction. In addition to improving bile flow, ursodiol may provide other protective effects. Over the past five years, several studies and case series in children have shown it to be beneficial, with a relatively mild adverse effect profile. Additional studies are needed to determine its benefit in improving hepatic function in children with biliary atresia and to define its role as prophylactic therapy in PNAC.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/23/09:

1. Alvimopan (Entereg®), a μ -opioid receptor antagonist used for improving GI motility after bowel resection, was added to the Inpatient Formulary.
2. Two new agents were added to the Outpatient Formulary: lanreotide depot (Somatuline® Depot), used in the management of acromegaly, and histrelin acetate (Supprelin LA®), used in patients with central precocious puberty.
3. The restrictions on tizanidine and polyethylene glycol 3350 (MiraLax®) were removed due to the availability of generic products.

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