CASE REPORT

Use of Ursodeoxycholic Acids in a Dog With Chronic Hepatitis: Effects on Serum Hepatic Tests and Endogenous Bile Acid Composition

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A dog with severe cholestasis secondary to chronic hepatitis was treated with ursodeoxycholic acid (UDCA) PO. After 2 weeks of daily treatment, the dog was more active and had an improved appetite. Monthly serum biochemical determinations and analysis of individual bile acid profiles documented improvement in hepatobiliary tests and a marked reduction in the concentrations of potentially hepatotoxic endogenous bile acids. These effects were maintained for approximately 6 months. The findings in this dog are similar to those reported for human patients treated with UDCA and provide preliminary evidence in support of its continued evaluation in the treatment of cholestatic liver disease in the dog.

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One consequence of cholestasis is the retention of constituents in bile. High concentrations of organic anions, notably bile acids, accumulate in the liver because of its critical function in their excretion. Prolonged exposure to high concentrations of hydrophobic bile acids (e.g., chenodeoxycholic acid) is cytotoxic to hepatocytes.[1] Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid with poorly defined properties thought to be protective for hepatocytes. Its use in human patients with cholestasis secondary to a variety of chronic liver diseases is associated with clinical and biochemical improvement.[2,3] The displacement of more hydrophobic bile acids from the bile acid pool by UDCA is one proposed explanation for its beneficial effect.[4]

We characterized sequential changes in serum bile acid profiles and biochemical analytes in a dog with severe cholestasis secondary to chronic hepatitis treated with UDCA orally. The objectives of the present study were to assess (1) the effect of treatment on composition of the serum bile acid pool, (2) the effect of treatment on hepatobiliary tests, and (3) the clinical value of treatment.

Case Report

A 9-year-old spayed female miniature schnauzer was referred for evaluation of icterus, decreased appetite, and occasional vomiting of approximately 3 weeks' duration. Prior management with a low-protein diet and antibiotics was not associated with clinical or biochemical improvement. A small liver was observed on radiographic and ultrasonographic examinations. Microscopic examination of a needle biopsy specimen of the liver was considered nondiagnostic. A patent common bile duct and a small liver with an irregular surface were noted while performing a celiotomy to obtain a second liver biopsy specimen. Histopathologically, severe fibrosis distorted the lobular architecture of the liver, and occasional portal-to-portal bridging was present. A mixed population of inflammatory cells was scattered throughout the fibrous tissue, and there was marked accumulation of yellow pigment. There was no growth of either aerobic or anaerobic bacteria after culture of hepatic tissue and bile.

Ursodeoxycholic acid (Actigal, Summit Pharmaceuticals, Division of CIBA-GEIGY, Summit, NJ) was given at a dosage of 15 mg/kg body weight PO sid. Serum samples were collected at monthly intervals before (2 months) and during (8 months) treatment. Prior to storage, samples were analyzed for activities of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase and concentrations of albumin, cholesterol, and total bilirubin. Results are presented in Table 1. Remaining portions of samples were frozen at −20°C for later analysis of serum bile acid concentrations. Serum sample preparation and analytic method have been described and validated for determination of concentrations of individual bile acids in canine serum.[5,6] Results for serum concentrations of selected bile acids are presented in Table 2.

Results

Approximately 2 weeks after beginning treatment with UDCA, the owner reported an improvement in the dog's appetite and activity, which was maintained for approximately 6 months. By the seventh month, serum aminotransferase activities and bilirubin concentration began to increase, and there was a progressive reduction in the serum albumin concentration (Table 1). Increasing lethargy and inappetence resulted in a request for euthanasia. Histopathologic findings in the liver were similar to those described for the biopsy specimen.

Two months before and at the start of treatment, serum concentrations of total bile acids were markedly increased (608 and 808 mol/L, respectively) (Table 2). Predominant forms were the more hydrophobic primary bile acids, taurocholic (TCA) and taurochenodeoxycholic (TCDCA) acids, which together constituted approximately 94% of the total concentration. Other bile acids with greater hydrophobicity also were detected. These included free and conjugated forms of lithocholic acid that were present in relatively low concentrations.

During the course of treatment with UDCA, concentrations of endogenous bile acids decreased markedly (205 mol/L at 6 months). Compared to serum concentrations at the start of treatment, those at 6 months posttreatment for TCA decreased >5.0-fold and those for TCDCA decreased ≥2.3-fold. These decreased concentra-

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Table 1. Serum Biochemical Findings in a Dog With Chronic Hepatitis Before and After Treatment With Ursodeoxycholic Acid

Month*	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Alb (g/dL)	Chol (mg/dL)	TB (mg/dL)
−2	572	99	3619	2.7	895	11.9
−1	307	115	5853	2.8	716	13.9
0†	490	104	5063	3.0	769	16.6
1	201	90	2265	3.2	540	9.9
2	167	123	2295	3.0	347	7.5
3	145	79	1694	2.9	216	5.8
4	138	88	1273	2.7	176	6.1
5	114	85	1061	2.6	124	6.1
6	127	123	959	2.4	100	5.0
7	130	140	597	2.3	65	7.7
Reference Range	10–88	8–52	20–110	2.4–3.8	125–270	0.1–0.6

* Month relative to the start of treatment with ursodeoxycholic acid.

† Start of treatment (ursodeoxycholic acid 15 mg/kg).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; Alb, albumin; Chol, cholesterol; TB, total bilirubin.

tions were accompanied by the appearance (at 1 month posttreatment) and continued presence of high concentrations (500 to 600 mol/L) of tauroursodeoxycholic acid (TUDCA), the major conjugated form of UDCA in the dog.

Discussion

These findings are consistent with those observed in human patients with chronic hepatitis treated with UDCA PO. A variety of mechanisms may be involved in producing these effects. Serum concentrations of total bile acids in healthy, fasted dogs and humans are <5 μmol/L. In contrast, total bile acid concentrations within hepatocytes and in the canalicular bile (measured in hepatic tissue from healthy humans) are approximately 50 μmol/L and 1,000 μmol/L, respectively.[7] Increased concentrations of cytotoxic hydrophobic bile acids develop in hepatic tissue with cholestasis.[8] Concentrations of CDCA similar to those measured in the serum of this dog (as TCDCA) are toxic to hepatocytes.[9] Ursodeoxycholic acid alters the enterohepatic circulation of endogenous bile acids by both hepatic and extrahepatic actions. Ursodeoxycholic acid does not suppress bile acid synthesis in humans or inhibit cholesterol 7α-hydroxylase activity.[10,11] This enzyme is rate limiting in the cholesterol–bile acid biosynthetic pathway and is inhibited by negative feedback secondary to the return of endogenous bile acids in portal blood.[12] The displacement of endogenous bile acids by UDCA may have an indirect permissive effect on bile acid production and produce a redistribution of the bile acid pool from the peripheral to the enterohepatic circulation.[11,13] An indirect indication of an UDCA-induced alteration in the enterohepatic circulation of bile acids is the rapid, marked decrease in serum cholesterol concentration, the substrate for bile acid synthesis. A modification of hepatic cholesterol metabolism at several steps and a direct inhibition of its intestinal absorption by UDCA have been proposed.[11,14–16]

Ursodeoxycholic acid also causes hypercholeresis, a unique physiologic property not associated with other common bile acids.[17–19] The decrease in serum bilirubin concentration may be a consequence of UDCA-enhanced bile flow. Other beneficial properties associated with UDCA include direct protective effects on hepatocellular membranes and subcellular components,[20–23] and immunomodulation.[24,25] The decrease in serum alanine aminotransferase activity is suggestive of improved hepatocellular membrane integrity.

The daily oral administration of UDCA to a dog with chronic hepatitis and severe cholestasis resulted in beneficial clinical and biochemical effects that were associated with decreases in concentrations of endogenous hydrophobic bile acids. These preliminary findings are similar to those documented in human patients with chronic hepatitis after treatment with UDCA, and support the continued evaluation of UDCA as a treatment of cholestatic liver disease in the dog.

Table 2. Concentrations of Selected Bile Acids in Serum of a Dog Treated With Ursodeoxycholic Acid

	Bile Acids (μmol/L)							
Month	UDCA	CA/GUDCA (coelute)	TUDCA	TCA	TCDCA	DCA + GDCA + TDC	Total	Total Endogenous
−2	0.0	0.5	0.7	468.9	105.9	1.7	607.9	606.7
−1	ND							
0*	1.4	1.6	0.5	598.5	157.9	3.6	808.0	804.4
1	20.2	0.9	493.7	483.6	116.4	1.9	1137.2	622.4
2	28.2	0.8	556.2	276.7	90.4	3.2	974.3	389.0
3	32.2	0.8	576.5	395.1	105.3	3.7	1135.9	526.4
4	31.6	0.3	605.6	190.9	76.6	3.6	923.6	286.0
5	8.1	0.4	572.7	158.1	74.4	2.0	833.3	252.2
6	11.9	0.4	520.6	118.6	66.7	1.5	737.5	204.6

* Start of treatment; UDCA 15 mg/kg PO q 24 h.

Abbreviations: UDCA, ursodeoxycholic acid; CA, cholic acid; GUDCA, glycoursodeoxycholic acid; TUDCA, tauroursodeoxycholic acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; DCA, deoxycholic acid; GDCA, glycodeoxycholic acid; TDCA, taurodeoxycholic acid.

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