Results of a Phase I Multiple-Dose Clinical Study of Ursodeoxycholic Acid

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Abstract

Background: The hydrophilic bile acid, ursodeoxycholic acid (UDCA), may indirectly protect against colon carcinogenesis by decreasing the overall proportion of the more hydrophobic bile acids, such as deoxycholic acid (DCA), in aqueous phase stool. In the AOM rat model, treatment with UDCA resulted in a significant decrease in adenoma formation and colorectal cancer. It was hypothesized that there is a dose-response relationship between treatment with the more hydrophilic bile acid, UDCA, and a reduction in the proportion of the more hydrophobic bile acid, DCA, in the aqueous stool phase, suggesting the potential of UDCA as a chemopreventive agent. Methods: Eighteen participants were randomized to 300, 600, or 900 mg/day UDCA for 21 days in this multiple-dose, double-blinded study. Seventy-two-hour stool samples were collected pretreatment and on days 18–20 of UDCA treatment for bile acid measurements. Pharmacokinetics were performed and blood bile acids were measured at days 1 and 21 of UDCA treatment. Results: There were no serious adverse events associated with UDCA treatment. There was a dose-response increase in the posttreatment to baseline ratio of UDCA to DCA from the 300 mg/day to the 600 mg/day group, but not between the 600 and the 900 mg/day groups, in both aqueous and solid phase stool. This posttreatment increase was statistically significant in aqueous phase stool for the 300 and 600 mg/day treatment groups (P = 0.038 and P = 0.014, respectively), but was only marginally significant in the 900 mg/day treatment group (P = 0.057). Following the first dose administration, a dose-dependent increase in plasma ursodeoxycholic concentrations was observed in fasting subjects; however, when these levels were measured postprandially following 3 weeks of treatment, the areas under the plasma concentration-time profile (AUC) were not statistically different and remained relatively unchanged over time. Conclusions: UDCA treatment did not decrease the quantity of DCA in fecal water or solids; however, it did decrease the proportion of DCA in fecal water and solids in relation to UDCA. Thus, 3 weeks of UDCA treatment resulted in an overall increase in hydrophilicity of bile acids in the aqueous phase stool, with a peak effect observed with a daily dose of 600 mg/day. Much larger studies are needed to determine the effect of ursodeoxycholic administration on deoxycholic concentration, overall hydrophilicity of stool bile acids, and the long-term effects on intermediate biomarkers of cellular damage. (Cancer Epidemiol Biomarkers Prev 2004;13(5):861–7)

Background

Bile acids are the most abundant end products of cholesterol metabolism. The primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesized in the liver and secreted into the bile. More than 95% of the primary bile acids are reabsorbed in the ileum, but a small percentage pass into the colon. In the colon, anaerobic bacteria metabolize primary bile acids and secondary bile acids are formed. Secondary bile acids, including deoxycholic acid (DCA) and lithocholic acid (LCA), are found in both the aqueous and solid portions of stool.

A variety of lines of evidence drawn from observations in animal and human trials support an important role of fecal bile acids in carcinogenesis. The carcinogenic potential of a bile acid was first reported in 1939 for DCA (1). In the ensuing years, further evidence has accumulated that supports an important role for certain bile acids as colon cancer promoters (2–6). In animal models, the bile acid CA acts in the promotion phase of carcinogenesis (7). Furthermore, bile acids increase colonic epithelial proliferation (8).

The mechanisms by which bile acids promote colon carcinogenesis are not completely understood. Secondary bile acids, such as DCA, have been reported to be cytotoxic to colonic epithelial cells (9–11), moderately mutagenic (12), associated with dysplastic changes (13), to stimulate PGE_2 synthesis (6), and to be anti-apoptotic (3, 5). Epidemiological research has associated colorectal cancer with high concentrations of bile acids in the stool, higher total fecal secondary bile acid concentrations (14, 15), and a higher concentration of DCA in fecal water (16).

A growing body of knowledge suggests that a reduction in concentration of membrane-toxic bile acids, such as DCA, in fecal water reduces epithelial cell injury

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and proliferation (3, 17, 18). The cellular toxicity of fecal water (detected by incubating fecal water with erythrocytes and measuring cell lysis) has been extensively evaluated and shown to be increased by factors that increase soluble bile acid concentrations and decreased by factors that reduce the DCA concentration (19–21). Several reports have suggested that factors affecting the relative concentrations of secondary bile acids (particularly DCA) in fecal water may be more important in altering the risk of colon cancer than those that simply modify the total fecal bile acid concentration (22–25). Additionally, a reduction in the concentration of membrane-toxic bile acids, such as DCA, in fecal water has been shown to reduce epithelial cell injury and proliferation (20, 21).

The growing body of evidence for the role of the various bile acids in colon carcinogenesis implicates the cytoprotective role of the more hydrophilic *versus* the cytotoxic role of the more hydrophobic bile acids. At high concentrations, the more hydrophobic bile acids, such as DCA and LCA, are known to be cytotoxic in the liver and to biliary epithelial cells by solubilizing polar lipids, leading to the disruption of plasma membranes (26). When administered p.o., the more hydrophilic bile acid, ursodeoxycholic acid (UDCA), becomes predominant in the bile acid pool, and decreases intestinal absorption of potentially toxic bile acids (26). Thus, the important factor may not be the actual quantity of each individual bile acid, but the proportion of hydrophilic *versus* hydrophobic bile acids that contributes to the overall hydrophilicity of aqueous stool, and therefore its cytotoxic/cytoprotective effects on the colonic mucosa. Aqueous stool bathes the colonic mucosa, and through direct contact affects the colonic epithelium. As implicated in research of the effects of bile acids in liver disease (27), the balance between the effects of toxic and non-toxic bile acids, however, may be only one determinant for colorectal cancer risk.

UDCA is a naturally occurring tertiary dihydroxy hydrophilic acid found in small quantities in normal human bile (about 5% of total bile acid). It is widely used for the treatment of primary biliary cirrhosis and other cholestatic disorders (28). UDCA is indicated to treat cholesterol gallstones and cholestatic liver disease. Over the past 20+ years of widespread clinical use, UDCA has developed a long history of safety. UDCA has been found to activate the metallothionein IIA promoter and other response elements in the HepG2 cell line, indicating its cytoprotective potential (29). It has been shown to decrease the relative proportion of DCA and to protect against DCA-induced apoptosis and proliferation in animal and human studies (3, 22, 30). UDCA administration has been associated with more than a 60% reduction in solid fecal DCA (22, 31, 32). In addition, UDCA feeding resulted in a highly significant inhibition of colorectal cancer and adenoma formation in the AOM-treated rat model (33). In this rat model, the feeding of UDCA also caused a 31% reduction in aqueous phase DCA. Supporting this work done in Arizona, a recent case-control study of patients with primary biliary cirrhosis found that long-term UDCA treatment was associated with a decreased probability of colorectal adenoma recurrence following removal (34).

The increase in the hydrophilic bile acids (such as UDCA) directly results in the proportionate decrease of the more hydrophobic bile acids (such as DCA) in stool, and therefore is hypothesized to increase the overall hydrophilicity of the colonic environment. If treatment with UDCA is able to increase aqueous phase hydrophilicity, this would demonstrate its potential for having a protective effect on the colonic epithelium. This phase I study attempts to evaluate the change in hydrophilicity of aqueous and solid stool as measured by the ratio of UDCA to DCA in stool of normal subjects treated with 300, 600, or 900 mg UDCA daily for 3 weeks.

Methods

Subjects. Eighteen healthy males and females between the ages of 18 and 80 years were randomized to one of three arms (300, 600, or 900 mg/day UDCA) in this multiple-dose, double-blinded study. Subjects were recruited through the Gastroenterology Clinic at the Arizona Health Sciences Center (AHSC) and through advertisements posted on AHSC notice boards. Each potentially eligible participant gave written informed consent according to institutional and federal guidelines. Eligible participants had no history of cancer within the past 5 years, adequate renal and liver function, an intact gall bladder, no history of large or small intestine surgery, and no life-threatening acute or chronic disease. Participants were asked to stop taking hypolipidemics and laxatives and to discontinue high-dose (≥1200 mg/day) calcium supplements during the course of the study. Participants were reimbursed US$125 to help defray the costs of transportation to the clinic and transportation of frozen stool specimens.

Study Procedures. Past medical history, gastrointestinal symptom history, a physical examination, dietary evaluation, and blood draw to determine eligibility were performed at baseline. A 2-week placebo run-in period was used to assess adherence to the treatment regimen. During the last 5 days of run-in, a standardized diet was consumed. This diet limited unusually high meat and fat intake that was outside normal dietary pattern and required that subjects record all foods and drinks consumed during the 5-day period. A 72-h stool collection was completed during the last 3 days of the run-in period. Participants were then randomly assigned to one of three UDCA dose levels: 300, 600, or 900 mg/day for a 21-day treatment period. During UDCA treatment, participants were instructed to record drug usage and adverse events in a study diary. Participants were provided with a copy of their dietary record from the run-in standardized diet on day 15 and were instructed to follow an identical diet for the last 5 days (days 16–20) of treatment. A second 72-h stool collection was completed during days 18–20. Toxicity evaluations were completed during clinic visits on days 1, 15, and 21 and over the phone on day 8. Toxicity evaluations captured information on nausea, vomiting, abdominal pain, diarrhea, and abnormalities in serum creatinine, hemoglobin, WBC, and liver enzyme profile.

Pharmacokinetics were performed on each subject on day 1 of UDCA treatment (single-dose fasting) and at day 21 of treatment (postprandial). The postprandial analysis followed a standard 'meal' of one container of

Ensure Fiber 1 h before the clinic visit baseline time point. Each pharmacokinetic blood draw was based on six time points: (1) at visit baseline; (2) 30 min; (3) 60 min; (4) 90 min; (5) 2 h; and (6) 4 h.

Stool samples were stored in metal containers, frozen, and transported on dry ice. Once in the laboratory, the samples were logged and stored at −80°C. For analysis, samples were first homogenized for 15 min with an equal volume of deionized water. Two ultracentrifuge tubes were filled and ultracentrifuged at a temperature of 4°C at a speed of 38,500 rpm for 1 h. The aqueous phase of the stool was removed, weighed, and placed into separate cryovials. Aqueous phase samples were also stored at −80°C. Only solid samples were lyophilized in a freeze-dryer according to manufacturer's instructions and stored at −80°C until shipment to the bile acid laboratory of Drs. A.K. Batta and Gerald Salen in Newark, NJ.

Gas chromatography (GC) of bile acids was carried out on a Hewlett-Packard model 6890 gas chromatograph equipped with a flame ionization detector and an injector with a split/splitless devise for capillary columns. The chromatographic column consisted of a chemically bonded fused silica CP-Sil-5 CB (stationary phase, 100% dimethylsiloxane) capillary column (25 m × 0.22 mm i.d.) (Chromopack, Raritan, NJ) and helium was used as the carrier gas. The gas chromatography operating conditions were as follows: injector and detector temperatures were 260°C and 290°C, respectively; after injection, oven temperature was kept at 100°C for 2 min, then programmed at a rate of 35°C/min to a final temperature of 278°C (22). The retention times of the *n*-butyl ester-trimethylsilyl esters of some of the bile acids relative to *n*-butyl ester-trimethylsilyl esters of nor-CA (retention time, 22.36 min) were as follows: *n*-butyl ester-trimethylsilyl ester of DCA, 1.119 and UDCA, 1.191.

Fecal bile acids were measured in 10–15 mg of freeze-dried solid phase stool (weighed exactly) or 100 μl aqueous phase stool. Internal standard (nor-CA, 20 mg) in 200 μl of *n*-butanol, followed by 50 μl concentrated hydrochloric acid was added and the contents were heated at 60°C for 4 h, followed by evaporation of solvents at 60°C (35). The residual product containing the *n*-butyl esters of bile acids was reacted with 100 μl of Silprep (hexamethyldisilazane:trimethylchlorosilane:pyridine, 3:1:9; Alltech Associated, Deerfield, IL) for 30 min at 55°C. Solvents were evaporated at 55°C under N_2 and the trimethylsilyl ether-*n*-butyl ester derivatives formed were dissolved in 200 ml of hexane and centrifuged. One to 2 μl of the clear supernatant was injected in the gas chromatography column. Bile acids were quantitated from the area under the curve relative to the internal standard. Nine randomly selected subjects had each of their stool samples re-analyzed for the six bile acids to assess the reliability of fecal bile acid measurements.

Concentrations of bile acids in blood were measured for each of the six time points both at baseline and at the end of UDCA treatment (time points: 1. visit baseline; 2. 30 min; 3. 1 h; 4. 90 min; 5. 2 h; and 6. 4 h). Nine subjects (50%) were re-measured to assess the reliability of pharmacokinetic analyses. A second random selection of nine subjects had each of their blood draws re-analyzed for each of the six bile acids to assess reliability of blood bile acid measurements.

Statistical Considerations. The primary treatment end point was defined as the ratio of UDCA to DCA (UDCA:DCA). This ratio was calculated for each participant, and the average change per group was reported. Means and SDs were computed within treatment groups for age, weight, and each bile acid. Mean bile acid concentrations for DCA and UDCAs were computed at baseline and posttreatment. Reliability of the stool bile acid measurements was estimated using repeated measures modeling. Paired *t* test analyses were performed on the difference between posttreatment and baseline for DCA, UDCA, and the per-participant ratio of UDCA:DCA. Non-detectable levels of bile acids were entered below the lowest detectable limit (0.05 mg/day aqueous and 0.3 mg/day solid).

Results

Fecal Bile Acids. Each of the 18 randomized participants successfully completed the study. The distributions of gender, age, and weight between treatment groups are summarized in Table 1. There were more women ($n = 13$) enrolled in the study than men ($n = 5$); however, there were no significant differences in the distribution of the genders across treatment groups. There were also no statistically significant differences for weight or age across treatment groups, although participants in the 900 mg/day group tended to be slightly older.

Table 2 presents the concentrations of UDCA and DCA in the aqueous and solid phases of stool collected from study participants. As expected, UDCA concentration increased with administration in all treatment groups.

Table 1. Distributions of sex, age, and weight across treatment groups

Variables	UDCA dose		
	300 mg/day	600 mg/day	900 mg/day
Gender*			
Male, *n*	2	2	1
Female, *n*	4	4	5
Age†, mean years (SD)	42.9 (15.7)	41.5 (9.2)	55.3 (8.7)
Weight‡, mean pounds (SD)	151.2 (16.0)	155.7 (13.0)	156.2 (36.4)

*$P = 0.770$, Cochran-Mantel-Haenszel test.
†$P = 0.306$, Analysis of variance test.
‡$P = 0.925$, Analysis of variance test.

A non-parametric (Kruskal-Wallis) test for imbalance showed no statistically significant differences in baseline DCA levels across treatment groups for either solid or aqueous phase stool. Repeated measures modeling showed high reliability of the stool bile acid measurements (UDCA 0.877; DCA 0.938).

The UDCA:DCA ratio is summarized across treatment groups in Table 3. As would be expected, the UDCA:DCA ratio increased across all treatment groups (0.42, 1.49, and 1.49 difference from baseline ratio in aqueous phase stool for the 300, 600, and 900 mg/day groups, respectively). However, this increase was only significant in aqueous phase stool in the 300 and 600 mg/day groups ($P = 0.038$ and $P = 0.014$, respectively). This difference was only marginally significant for the 900 mg/day group ($P = 0.057$). Nine subjects had undetectable levels of UDCA in aqueous stool at baseline, three from each treatment group. One subject had undetectable levels of UDCA in solid stool at baseline (600 mg/day group). In all cases of undetectable bile acids, the value was set below the lowest detectable limit.

Plasma Bile Acids. Table 4 summarizes the fasting pretreatment baseline UDCA concentrations among treatment groups and the pre-dose plasma UDCA concentrations determined following a liquid meal on the last treatment day. There were no significant differences in the pre-dose UDCA concentrations across treatment groups determined before the initiation of the 3-week treatment or determined postprandially before the administration of the last dose of UDCA. The predose plasma UDCA levels measured postprandially following the 3 weeks of UDCA treatment were significantly higher than those determined under fasting conditions before the initiation of 3 weeks of treatment ($P < 0.05$).

Figures 1 and 2 illustrate the average plasma UDCA concentrations *versus* time profiles at different dose levels. The average fasting predose plasma UDCA concentrations were 0.95, 0.25, and 0.58 μg/ml for subjects assigned to the 300, 600, and 900 mg dose level, respectively. In the fasting state, plasma UDCA concentrations, measured up to 240 min post-administration, increased over time or increased to a peak level and declined as a function of time. At 240 min after the first day's administration of the 300, 600, and 900 mg doses of UDCA, the average plasma concentrations were 1.88, 1.80, and 2.05 μg/ml, respectively. Although plasma UDCA concentrations determined postprandially remained relatively unchanged as a function of time after the day 21 UDCA dose, there were clear upward trends. The average pre-dose plasma UDCA concentrations determined postprandially following 3 weeks of daily administration were 2.78, 3.22, and 4.63 μg/ml, respectively, and at 240 min after administration of the last dose of UDCA, the average plasma levels were 3.02, 4.26, and 5.62 μg/ml, respectively, in the 300, 600, and 900 mg dose group.

The AUC of UDCA from 0 to 240 min after dosing was estimated using the model-independent approach and the resulting calculations are summarized in Table 5. The average plasma AUC determined after the first dose in fasting subjects was 354.5, 474.7, and 652.2 [(μg/ml)·min] in the 300, 600, and 900 mg dose group, respectively. The average AUC determined after the last dose in non-fasting subjects was 737.2, 947.8, and 1105.9 [(μg/ml)·min] in the 300, 600, and 900 mg dose group, respectively. There was an approximate 2-fold increase in AUC across all groups from day 1 to day 21, but because of large interindividual variability, no statistically significant dose-dependent increase in plasma AUC could be found following the first dose administration and the last dose administered on day 21. At the 300 mg dose level, mean AUC determined postprandially following 3 weeks of UDCA treatment was significantly higher than that determined under fasting conditions after administration of one dose.

Toxicities. Nine subjects (50%) did not experience any adverse events. The remaining nine subjects experienced gastrointestinal symptoms including mild constipation (6% incidence), mild to moderate loose stools/soft stools/diarrhea (39%); mild gastritis (6%); mild lower abdominal pain/cramps (22%); and mild nausea (11%). Gastrointestinal toxicities were experienced by two subjects (33%) receiving 300 mg/day UDCA, five subjects (83%) receiving 600 mg/day UDCA, and two subjects

Table 2. Mean bile acid concentrations at baseline and after treatment with UDCA in aqueous and solid phase stool

	UDCA	DCA
(A) Aqueous phase stool bile acid concentrations (mg/day), mean (SD)		
Baseline		
300 mg/day	0.368 (0.474)	4.077 (6.113)
600 mg/day	1.202 (1.338)	9.387 (6.856)
900 mg/day	0.242 (0.299)	4.072 (1.573)
Posttreatment		
300 mg/day	1.730 (1.922)	4.525 (5.890)
600 mg/day	25.905 (26.197)	13.187 (12.111)
900 mg/day	13.507 (20.323)	8.263 (6.068)
(B) Solid phase stool bile acid concentrations (mg/day), mean (SD)		
Baseline		
300 mg/day	5.527 (5.621)	84.865 (18.755)
600 mg/day	8.880 (7.103)	100.195 (37.142)
900 mg/day	5.132 (3.074)	101.235 (38.725)
Posttreatment		
300 mg/day	29.223 (22.817)	58.350 (36.483)
600 mg/day	220.130 (148.377)	77.665 (61.477)
900 mg/day	136.530 (126.633)	102.487 (57.783)

Table 3. Mean ratio (SD) of UDCA to DCA in aqueous and solid phase stool: baseline to posttreatment

	Aqueous phase	Solid phase
Baseline UDCA:DCA (SD)		
300 mg/day ($n = 6$)	0.12 (0.14)	0.08 (0.10)
600 mg/day ($n = 6$)	0.10 (0.09)	0.08 (0.04)
900 mg/day ($n = 6$)	0.10 (0.02)	0.06 (0.06)
Posttreatment UDCA:DCA (SD)		
300 mg/day ($n = 6$)	0.54 (0.47)	0.75 (0.77)
600 mg/day ($n = 6$)	1.58 (1.05)	3.86 (4.29)
900 mg/day ($n = 6$)	1.59 (1.51)	1.62 (1.69)
UDCA2:DCA2-UDCA1:DCA1*		
300 mg/day ($n = 6$)	0.42 ($P = 0.038$)†	0.66 ($P = 0.062$)
600 mg/day ($n = 6$)	1.49 ($P = 0.014$)†	3.78 ($P = 0.083$)
900 mg/day ($n = 6$)	1.49 ($P = 0.057$)	1.56 ($P = 0.073$)

*UDCA1 = baseline UDCA; UCDA2 = posttreatment UDCA; DCA1 = baseline DCA; DCA2 = posttreatment DCA.
†Statistically significant.

Table 4. Mean baseline plasma UDCA concentrations (μg/ml) determined in fasting subjects before the administration of the first dose of UDCA and mean plasma UDCA following a liquid meal on the last treatment day UDCA

	300 mg/day	600 mg/day	900 mg/day
	Mean ± SD	Mean ± SD	Mean ± SD
Mean baseline plasma UDCA	0.95 ± 0.96	0.25 ± 0.25	0.58 ± 0.39
Mean plasma UDCA on last day of treatment	2.78 ± 1.54*	3.22 ± 1.85*	4.63 ± 2.05*

*Significantly different from the corresponding fasting pretreatment levels, $P < 0.05$.

(33%) receiving 900 mg/day UDCA. Other adverse events possibly related to UDCA therapy included: grade 1 back pain (n = 1, 600 mg dose); a grade 2 dermatological reaction (n = 1, 600 mg dose); and grade 1 metallic taste (n = 1, 600 mg dose).

Discussion

In both experimental animal and human studies, secondary bile acids, such as DCA, have been shown to enhance colonic epithelial cell proliferation, to be cytotoxic to colonic epithelial cells (9–11), and moderately mutagenic (12). In contrast, UDCA inhibited colorectal cancer and adenoma formation in AOM-induced rat models (33). Rats that received UDCA at a dose of 0.4% had a 50–88% reduction in the concentration of DCA in the aqueous phase of stool compared to control animals (36). While the exact mechanisms for action of UDCA are not known, it has been suggested that as well as diluting the concentration of DCA in the stool, UDCA interferes with the 7-α-dehydroxylation of CA, thereby slowing secondary bile acid formation (37).

The results of this study show that treatment with UDCA in human subjects did not result in a decrease in the amount of DCA, but did decrease the proportion of DCA to UDCA when compared with baseline levels in all treatment groups. The results were consistent in both solid and aqueous phase stool, but the only statistically significant difference was in aqueous stool at the 300 and 600 mg/day dose levels. The values listed in Tables 2 and 3 demonstrate that administration of UDCA dilutes the concentration of DCA in the aqueous stool without decreasing its absolute concentration.

Measurement of bile acids was highly reliable, but there is high biological variability in fecal bile acid concentrations. The lack of a statistically significant increase in the ratio of UDCA to DCA with the 900 mg/day dose is likely due to the large SD in that group. It is unlikely that the 900 mg dose produced any different metabolites as compared to 300 or 600 mg doses that would account for the lack of significance in that group. All doses of UDCA are relatively small so that a large proportion of UDCA will always be metabolized by intestinal bacteria without saturating bacteria capacity, and it will be metabolized similarly whether given in a dose of 300, 600, or 900 mg to the same individual.

UDCA was not associated with any severe toxicity. There were no study withdrawals related to an adverse event, and there was no evidence of a dose-dependent increase in toxicity. All reported symptoms resolved spontaneously or were considered to be unrelated to study treatment and referred to primary care physicians for follow up.

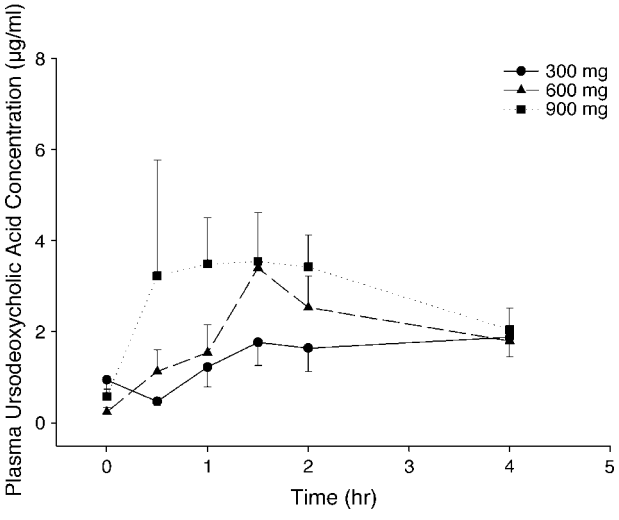

Figure 1. Pretreatment, fasting pharmacokinetics. Mean plasma UDCA *versus* time profiles following the administration of the first dose of 300, 600, or 900 mg UDCA in fasting subjects.

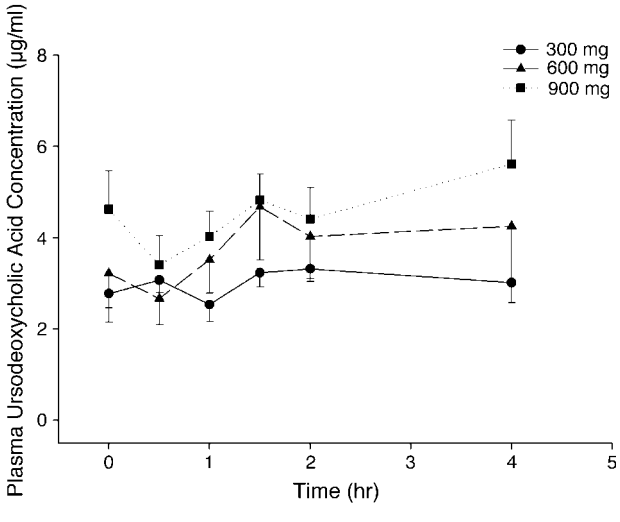

Figure 2. Post-treatment, postprandial pharmacokinetics. Mean plasma UDCA *versus* time profiles after the last dose of UDCA following 3 weeks of daily treatment of 300, 600, or 900 mg/day. Study subjects had received a liquid meal before the last dose of UDCA.

Table 5. Area under the plasma concentration-time profile of UDCA [(μg/ml)·min] determined from time 0 to 240 min after dosing

300 mg/day		600 mg/day		900 mg/day	
Mean ± SD		Mean ± SD		Mean ± SD	
Fasting*	Postprandial†	Fasting*	Postprandial†	Fasting*	Postprandial†
354.5 ± 213.5	737.2 ± 149.9‡	474.7 ± 247.6	947.8 ± 498.9	652.2 ± 505.8	1105.9 ± 287.9

*Posttreatment, fasting; determined following the administration of the first dose of UDCA in fasting subjects.
†Posttreatment, postprandial; determined after the last dose of UDCA following 3 weeks of daily treatment. Study subjects had received a liquid meal before the last dose of UDCA.
‡Significantly different from the pretreatment AUC value at the same dose level, $P < 0.05$.

As observed in this study, the administration of UDCA decreased the proportion of DCA in fecal water, which reflects the overall increase in hydrophilicity of bile acids in the aqueous phase stool. Much larger studies are needed to determine the effect of UDCA administration on DCA concentration, overall hydrophilicity, and the long-term effects on intermediate biomarkers of cellular damage. Such colorectal adenoma prevention studies have been initiated at the Arizona Cancer Center in 1285 participants with a history of resected colorectal adenomas, the results of which will be published in a future manuscript.

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