CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020675

PHARMACOLOGY REVIEW(S)

Strongin

NDA 20-675 Page 1

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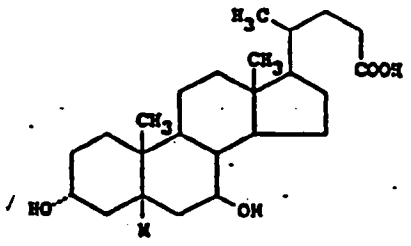
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

DRUG: Ursodiol (URSO™, 250 mg tablet), ursodeoxycholic acid, RU 22990.

(3α,5β,7β)-3,7-Dihydroxycholan-24-oic acid



$C_{24}H_{40}O_4$ MW 392.56

FORMULATION: Tablet consisting of core (250 mg of ursodeoxycholic acid, [redacted] of microcrystalline cellulose [redacted] of povidone [redacted] of polyethylene glycol 3350 [redacted] of sodium starch glycolate [redacted] of magnesium stearate NF) and coating (hydroxypropyl methylcellulose [redacted] dibutyl sebacate [redacted] polyethylene glycol 8000 [redacted] and carnauba wax NF).

CATEGORY: Bile Acid.

PROPOSED MARKETING INDICATION: URSO™ tablets are indicated for the treatment of patients with all stages of primary biliary cirrhosis (PBC).

DOSE: Recommended daily adult doses range from 4 to 7 tablets (20 to 35 mg/kg in a 50 kg individual) in four divided doses.

PRECLINICAL STUDIES AND TESTING LABORATORIES:

Type of Study	Study/Report #	Testing Laboratory	Drug Batch #	Review Page #
Pharmacology	---	---	---	4
Absorption, Distribution, Metabolism & Excretion: Mice, rats & monkeys	---	---	---	14
Acute toxicity-i.v.-mice	---	[redacted]	---	34
Acute toxicity-i.p.-mice	---		---	34
Acute toxicity-s.c.-mice	---		---	34
Acute toxicity-p.o.-mice	---		---	34
Acute toxicity-i.v.-rats	---		---	35
Acute toxicity-i.p.-rats	---		---	35
Acute toxicity-s.c.-rats	---		---	35
Acute toxicity-p.o.-rats	---		---	35
Acute toxicity-p.o.-hamsters	---		110 7987	35
Acute toxicity-p.o.-dogs	---		110 7987	35
5-week i.p. toxicity in rats	---		---	37
5-week p.o. toxicity in rats	---		---	40
6-month p.o. toxicity in rats	---		110 7987	42
6-month p.o. toxicity in rats	---		---	44
6-month p.o. toxicity in monkeys	---		---	47
1-year p.o. toxicity in monkeys	---		---	49

Carcinogenicity				
104-week dietary carcinogenicity in mice	406-006	[redacted]	33, 37, 38	54
104-week dietary carcinogenicity in mice	536		AL-80	62
103-week oral carcinogenicity of lithocholic acid in mice	NCI-CG-TR-175		---	69
104-week dietary carcinogenicity in rats	537		AL-80	74
126 to 138-week dietary carcinogenicity in rats	---		110 7987	85
103-week oral carcinogenicity of lithocholic acid in rats	NCI-CG-TR-175		---	94
Mutagenicity				
Ames assay	---	[redacted]	---	104
Mouse lymphoma forward mutation assay	---		110 7987	104
Sister chromatid exchange assay in human lymphocytes	---		---	106
Mouse spermatogonia chromosomal aberrations	---		---	107
Chinese hamster micronucleus test	---		---	108
Chinese hamster bone marrow cell chromosomal aberrations	---		---	108
Reproductive Toxicology				
Segment I. Oral fertility and reproductive performance study in rats	---	[redacted]	KG 85	109
Segment I. Oral fertility and reproductive performance study in rats	---		---	114
Segment II. I.p. teratology study in mice	---		---	119
Segment II. Oral teratology study in mice	---		---	121
Segment II. I.p. teratology study in rats	---		---	124
Segment II. Oral teratology study in rats	---		---	126
Segment II. Oral teratology study in rats	---		---	129

Segment II. Oral teratology study in rabbits	---	LPT	---	133
Segment II. Oral teratology study in rabbits	---	KU	---	135
Segment III. Oral perinatal and postnatal study in rats		KU	---	137

[redacted]

PHARMACOLOGY:

The pathogenesis of primary biliary cirrhosis (PBC) involves the evolution of (1) inflammation of medium-sized bile ducts, (2) periportal fibrosis, (3) progressive scarring, and (4) firm, regular, intensely bile-stained cirrhosis. Signs and symptoms of PBC usually include pruritus and/or nonspecific fatigue; enlarged, firm, nontender liver; jaundice; cholestasis with elevation of alkaline phosphatase; elevated serum bile acid concentrations and activity of serum γ-glutamyl transpeptidase; possible elevation of serum cholesterol; and antibodies against a component of the inner membrane of mitochondria.

The etiology of PBC is not clear. The presence of antibodies against a component of the inner membrane of mitochondria have prompted many clinicians to view PBC as an autoimmune disease. Thus, historically, attempts have been made to treat PBC with immune modulators such as azathioprine, cyclosporine, chlorambucil and prednisone. These agents were relatively ineffective or too toxic. Currently, liver transplantation appears to the only viable treatment for PBC.

Obviously, the signs and symptoms of PBC suggest that bile acids might either play a role in the pathogenesis of PBC or might produce symptoms of PBC that could be reduced by modifying physiological and biochemical effects of bile acids through pharmacological treatment. The sponsor has referred to published clinical studies which suggest that ursodeoxycholic acid (UDCA) has significant therapeutic effects in patients with PBC. Beneficial effects of a pharmacological agent for PBC might include any reduction of the signs and symptoms of PBC such as alleviation of pruritus, enlarged liver and jaundice; the reversal of cholestasis; and the reduction of serum and bile levels of any contributing biological substance.

Primary Pharmacology

1. In Vitro Studies:

Cholesterol uptake into rat jejunal retroverted sacs

Cholesterol uptake into rat jejunal retroverted sacs from micellular solutions containing cholesterol and bile salts [either taurochenodeoxycholate (TCDC, 10 mM-oleate or 3.6 mM-monoolein), taurocholate (TC, 10 mM-oleate or 3.6 mM-monoolein) or tauroursodeoxycholate (TUDC, 10 mM-oleate or 3.6 mM-monoolein)] was primarily dependent on cholesterol saturation of micelles. Cholesterol uptake was reduced by -76%, -62% and -62% in the presence of TUDC, TCDC and TC, respectively.

Bile acids in isolated baboon livers

In isolated baboon livers perfused with diluted human blood, the addition of chenodeoxycholic acid (CDCA, concentration was not provided) to the perfusate decreased bile flow (-11%), while ursodeoxycholic acid (UDCA, concentration was not provided) and cholic acid (CA, concentration was not provided) had no effect. Cholesterol specific activity increased to 77.9, 61.1 and 48.7 dpm/nmol during CA, CDCA and UDCA infusion, respectively; thus, *de nova* synthesis of biliary cholesterol was relatively less during UDCA perfusion. Relative biliary phospholipid content was greater during UDCA perfusion (19.9% of total biliary lipids) than during CA (5.3%) and CDCA (11.4%) perfusion.

In another study in which isolated baboon livers were perfused with diluted human blood, the addition of chenodeoxycholic acid (CDCA, 1 μmol/h/g) to the perfusate decreased bile flow (approximately -75%), while ursodeoxycholic acid (UDCA, 1 μmol/h/g) and cholic acid (CA, 1 μmol/h/g) had little or no effect. CDCA and UDCA decreased cholesterol synthesis (approximately -30 to -40%), and UDCA increased biliary phospholipid level (data was not provided).

Bile acids in isolated perfused rat livers

In isolated perfused rat livers, either taurochenodeoxycholate (TCDC, 56 μmol over 90 min) or tauroursodeoxycholate (TUDC, 56 μmol over 90 min) increased bile flow, bile salt output, biliary phospholipid output, and biliary enzyme (5'-nucleotidase and alkaline phosphodiesterase I) output (data were summarized in figures; quantitative data were not provided).

2. In Vivo Studies:

A. Intravenous administration of ursodeoxycholic acid

Rats

Bile flow and biliary acid levels

Male rats were intravenously infused with either taurocholate (570-1280 nmol/min/100 g body weight), 7-ketolithocholate (500-670 and 900-1590 nmol/min/100 g body weight), ursodeoxycholate (960-1660 nmol/min/100 g body weight), cholate (560-750 nmol/min/100 g body weight), dehydrocholate (900-1200 nmol/min/100 g body weight) or deoxycholate (660-870 nmol/min/100 g body weight). Bile flow (μl/min/100 g) in the presence of the above bile acids was increased by 87%, 52 and 174%, 161%, 66%, 173% and 42% (% of difference from control), respectively. Total biliary acid levels (mM) were increased by 150%, 26 and 88%, 8%, 75%, 53% and 62%, respectively.

Biliary transport, bile flow and bile salt excretion rate

Male rats were intravenously infused with either ursodeoxycholate (UDC, 0.6 to 2.8 μmol/min/100 g body weight) or glycoursodeoxycholate (GUDC, 0.6 to 2.8 μmol/min/100 g body weight). In the case of GUDC, the estimated maximum biliary transport value was 2.21 μmol/min/100 g body weight; there was a linear relationship between bile flow and bile salt excretion rate (slope value of 4.10 μl/μmol). On the other hand, in the case of UDC, the relationship between bile flow and bile salt excretion rate gradually changed; as bile flow increased, there was a sharp drop in excretion of the UDC conjugate taurodeoxycholic acid.

Male rats were intravenously infused with either tauroursodeoxycholate (TUDC, 0.6-1.8 μmol/min/100 g body weight) or taurocholate (TC, 0.6 μmol/min/100 g body weight). TUDC increased bile flow rate (μl/min/100 g) by 44-62% (% of difference from control), while TC increased bile flow rate by 64%. TUDC increased the biliary transport maximum (BSP T_m) of sulfobromophthalein by 22-35%, while TC increased the BSP T_m by 66%.

Male rats were intravenously infused with either ursodeoxycholate (UDC), tauroursodeoxycholate (TUDC), cholate (C), taurocholate (TC) or UDC in the presence of taurine at progressively increasing rates. The biliary maximum secretory rate (SR_m, nmol/min/100 g body weight) was 1,835.2 and 1,749.4 for TC and C, respectively. On the other hand, the SR_m was 5,909.4 and 802.1 for TUDC and UDC, respectively. The SR_m for UDC in the presence of taurine (1,367) was higher than for UDC, but lower than for TUDC.

Dogs

Bile flow, biliary excretion and hepatic blood flow

Male dogs were intravenously administered single doses of 3, 10 and 30 mg/kg of dehydrocholic acid (DHCA), ursodeoxycholic acid (UDCA) and chenodeoxycholic acid (CDCA), respectively. All bile acids dose-dependently increased volume of hepatic bile flow with order of potency being DHCA>UDCA>CDCA (data were summarized in figures; quantitative data were not provided). There was no relationship between bile acid excretion and hepatic blood flow.

Rabbits

Bile volume and HCO_3^- concentration

Male rabbits were intravenously infused (0.4 μmol/min/100 g body weight) with deoxycholate (DC), chenodeoxycholate (CDC), taurochenodeoxycholate (TCDC), cholic acid (CA), tauroursodeoxycholic acid (TUDCA) and ursodeoxycholic acid (UDCA), respectively, for 30 min followed by infusion at a rate of 0.8 μmol/min/100 g body weight for an additional 30 min. All bile acids except TCDC increased bile volume with a potency order of DC>UDCA and TUDCA>CDC>TCDC (quantitative data were not provided). The concentration of HCO_3^- was increased by DC, UDCA and CDC, but not by the other bile acids.

B. Oral administration of ursodeoxycholic acid

Mice

Hepatic and serum cholesterol levels

Mice were fed cholesterol-free diet containing 0.5% ursodeoxycholic acid (UDCA) for 10 days; a control group was fed cholesterol-free diet without UDCA supplementation. At the end of treatment, serum cholesterol levels were decreased by 44% (% of difference from control) in UDCA-treated animals. At sacrifice, hepatic cholesterol was 8.07 mg/g liver in controls and 6.43 mg/g liver in UDCA-treated animals.

Rats

Hepatic bile acids and alkaline phosphatase activity; serum alkaline phosphatase activity

Bile acid pools were drained in biliary fistulated rats for 6 h; bile flow was then obstructed for the following 12 h. Taurocholate (TC), taurochenodeoxycholate (TCDC) or tauroursodeoxycholate (TUDC) were intravenously infused (35 μmol/100 g) for the first 2 h of obstruction. Hepatic bile acids (μg/g liver) were increased by 225% (% of difference from obstructed controls receiving diluent) by TC. Hepatic alkaline phosphatase (μmol P_i/mg/prot/h) was increased by 293%, 207% and 171% (% of difference from obstructed controls receiving diluent) by TC, TCDC and TUDC, respectively. Serum alkaline phosphatase (μmol P_i/100 μl) was increased by 315% and 169% by TC and TCDC, respectively; TUDC had no effect. Thus, increases in alkaline phosphatase are associated with retention of TC and TCDC, but not TUDC.

Effects of dietary UDCA on total bile acids

Male rats were fed diet containing 1.29 mg/g of cholesterol and 0.99 mg/g of β-sitosterol. In one group, the diet was further supplemented with 0.5% ursodeoxycholic acid (UDCA); a second group (controls) did not receive supplemental UDCA. UDCA treatment increased body weight gain, but had no effect on cholesterol concentration in liver, plasma and bile. In UDCA-treated animals, UDCA was the predominant bile acid (67% of total bile acids). In controls, cholic acid (CA), chenodeoxycholic acid (CDCA) and α- and β-muricholic acid represented 41%, 41% and 14% of total bile acids, respectively. In animals given UDCA supplementation; CA, CDCA and α- and β-muricholic acid were reduced to 3%, 19% and 0% of total bile acids, respectively. ω-Muricholic acid (7% of total bile acids) and lithocholic acid (1% of total bile acids) were found in bile of UDCA-treated animals, while they were undetectable in controls. Bile concentrations of deoxycholic acid were not affected by UDCA treatment.

Effects of UDCA on ethinyl estradiol-induced biliary cholesterol levels

Male rats received ethinyl estradiol (EE, 5 mg/kg, s.c.), ursodeoxycholic acid (UDCA, 15 mg/kg/day, p.o.), EE plus UDCA, and vehicle, respectively, for 7 days. EE produced a 53% increase in biliary cholesterol level (% of difference from control), while UDCA produced a -16% decrease in biliary cholesterol level. In the EE plus UDCA group, biliary cholesterol level was not significantly different from that in controls.

Dogs

Biliary phospholipid levels and total bile acids

Male dogs were orally administered single 50 mg/kg doses of ursodeoxycholic acid (UDCA), chenodeoxycholic acid (CDCA) and dehydrocholic acid (DHCA), respectively. UDCA and CDCA significantly increased biliary phospholipid levels by 141% (% of difference from control) and 119%, respectively; DHCA had no effect. None of the bile acids affected biliary cholesterol and bilirubin levels. Biliary UDCA output levels before UDCA administration were zero; biliary UDCA output levels were 62.7 mg/h after UDCA administration. Biliary CDCA output levels before CDCA administration were 7.9 mg/h; biliary CDCA output levels were 94.4 mg/h after CDCA administration. The metabolite 3α,7α-dihydroxy-12-keto-cholanoic acid was undetectable in the bile before oral bile acid administration; biliary 3α,7α-dihydroxy-12-keto-cholanoic acid output levels were 30.2 mg/h after DHCA administration, but were undetectable after UDCA and CDCA administration.

Hamsters

Interactions of cholesterol, ethinyl estradiol and bile acids on formation of gallstones

Two groups (I and II) of female hamsters were fed diet containing 0.8 mg cholesterol/g for 12 weeks; Group II also received 15 μg/kg/day of ethinyl estradiol. Four other groups (III, IV, V and VI) were fed diet containing 2.4 mg cholesterol/g of food for 12 weeks; Group IV also received 15 μg/kg/day of ethinyl estradiol; Group V also received 15 μg/kg/day of ethinyl estradiol plus 20 mg/kg/day of chenodeoxycholic acid (CDCA); Group VI also received 15 μg/kg/day of ethinyl estradiol plus 20 mg/kg/day of ursodeoxycholic acid (UDCA). Groups I, V and VI had no gallstones, while 30%, 50% and 90% of animals had gallstones in Groups II, III and IV, respectively. Bile was saturated in Groups II, III and IV, but not in Groups V and VI. Groups V and VI that were fed CDCA and UDCA had decreased hepatic HMG-CoA reductase and cholesterol 7α-hydroxylase activities.

One group (I) of female hamsters was fed diet containing 0.8 mg cholesterol/g of food for 12 weeks. Five other groups (II, III, IV, V, and VI) were fed diet containing 2.4 mg cholesterol/g of food plus 15 μg/kg/day of ethinyl estradiol for 12 weeks. During the subsequent 8 weeks; Group I was fed diet containing 0.8 mg cholesterol/g of food; Group II, diet containing 2.4 mg cholesterol/g of food plus 15 μg/kg/day of ethinyl estradiol; Group III, diet containing 0.8 mg cholesterol/g of food; Group IV, diet containing 2.4 mg cholesterol/g of food plus 15 μg/kg/day of ethinyl estradiol plus 20 mg/kg/day chenodeoxycholic acid (CDCA); Group V, diet containing 2.4 mg cholesterol/g of food

plus 15 μg/kg/day of ethinyl estradiol plus 20 mg/kg/day ursodeoxycholic acid (UDCA), and Group VI; diet containing 2.4 mg cholesterol/g of food plus 15 μg/kg/day of ethinyl estradiol plus 20 mg/kg/day cholic acid (CA). Groups I, IV and V had no gallstones, while 90%, 90% and 80% of animals had gallstones in Groups II, III and VI, respectively. Bile was not saturated in Groups IV and V. Groups IV and V that were fed CDCA and UDCA had decreased hepatic HMG-CoA reductase activity.

Interactions of cholesterol, ethinyl estradiol, terpenes and UDCA on formation of gallstones

One Group (I) of female hamsters was fed diet containing 2.4 mg cholesterol/g of food plus 15 μg/kg/day of ethinyl estradiol (lithogenic regime, LR) for 12 weeks; Group II, LR plus 20 mg/kg/day ursodeoxycholic acid (UDCA); Group III, LR plus 5 mg/kg/day mixed terpenes; Group IV, LR plus 10 mg/kg/day mixed terpenes; Group V, LR plus 20 mg/kg/day mixed terpenes; Group VI, LR plus 10 mg/kg/day Rawachol (mixture of terpenes in olive oil); Group VII, 0.2 ml/day olive oil; and Group VIII, standard diet. Rawachol reduced HMG-CoA reductase activity by 18%, but did not dissolve gallstones. Neither the mixed terpenes nor Rawachol altered the biliary cholesterol saturation index, bile acid pool size or cholesterol 7-α hydroxylase activity or prevented gallstone formation. On the other hand, UDCA did not saturate the bile, increased total bile acid pool size by 38%, depressed HMG-CoA reductase activity by 29%, and prevented gallstone formation.

C. Intrajejunal administration of ursodeoxycholic acid

Hamsters

Cholesterol saturation

Male hamsters were intrajejunally infused (26 μmol/h for 6 h) with either taurocholic acid (TCA), taurochenocholic acid (TCCA), or tauroursocholic acid (TUCA). The % cholesterol saturation was 31%, 56% and 54% for TCA, TCCA and TUCA, respectively.

Secondary Pharmacology:

1. In Vitro Studies:

Rats

Gastrointestinal effects

Colonic absorption and secretion

When isolated rat colons were perfused with ursodeoxycholic acid (UDCA, 2.5 and 5.0 mM) and chenodeoxycholic acid (CDCA, 2.5 and 5.0 mM), respectively, absorption of water was reversed by CDCA into secretion (1.1-2.5 ml/15 min/g dry wt.) to a greater extent than by UDCA (0-0.8 ml/15 min/g dry wt.). CDCA also reversed

absorption of sodium into secretion (135-300 μmol/15 min/g dry wt.) to a greater extent than UDCA (0-50 μmol/15 min/g dry wt.). Oxalate absorption and permeability of the colon measured by disappearance of D-mannitol was enhanced by CDCA, but not by UDCA. Thus, one would predict that CDCA might contribute to the emergence of diarrhea, while UDCA probably would not.

Liver

Hepatic alkaline phosphatase activity

The ability of bile acids to induce synthesis of alkaline phosphatase was assessed in rat liver cell cultures. Taurocholate (TC, 0.1-1.0 mM) induced dose-related increases in alkaline phosphatase (0-65%, % of difference from control) in bile. Taurochenodeoxycholate and taurodeoxycholate (0.1-1.0 mM) produced similar increases in alkaline phosphatase to that produced by TC, while tauroursodeoxycholate (0.1-1.0 mM) produced a maximum increase of only 30%. Since PBC is usually associated with elevation of alkaline phosphotase, any further increases produced by taurine conjugates of bile acids would most likely be undesirable.

2. In Vivo Studies:

A. Gastrointestinal tract

Rats

Gastrointestinal secretion

When an isolated *in vivo* cecal loop technique was employed in rats, 4 mM concentrations of deoxycholic acid and chenodeoxycholic acid produced significant secretion of water (49.4 and 34.1 μl/min/g, respectively) and sodium (5.75 and 3.30 μEq/min/g, respectively). A similar concentration of ursodeoxycholic acid had no effect.

When the proximal jejunum of rats was perfused *in vivo* with 0.5 mM chenodeoxycholic acid, there was an accumulation of net luminal water (0.734 μl/cm/min); while 0.5 mM ursodeoxycholic acid led to water secretion (0.444 μl/cm/min) out of the jejunum.

Bile acid contents of colonic lumen and wall

Female rats were fed 90 mg/kg/day of chenodeoxycholic acid (CDCA) and ursodeoxycholic acid (UDCA), respectively, for 14 days. When rats were sacrificed and bile acids were measured in colonic contents and colonic wall, total increases of bile salts in colonic contents were similar after CDCA and UDCA administration with more bile acid sulfate esters after CDCA administration and

more lithocholic acid after UDCA administration. Total nonsulfated bile acids in colonic mucosa rose from 16.96 μg/g (mean basal level) to 20.22 μg/g after CDCA administration and to 35.80 μg/g after UDCA administration.

Rabbits

Effects of bile acids on adenylate cyclase activity, net secretion and cGMP activity in isolated ileum and colon

When isolated *in vivo* ileal and colonic loop techniques were employed in rabbits, 6 mM concentrations of deoxycholic acid (DCA) and chenodeoxycholic acid (CDCA) increased adenylate cyclase activity and net secretion and decreased cGMP activity (data were presented in figures; quantitative data were not provided). In contrast, a 6 mM concentration of ursodeoxycholic acid (UDCA) had no effect on adenylate cyclase activity and net secretion, but increased cGMP activity. Thus, physiological responses mediated by adenylate cyclase activity are apparently enhanced by DCA and CDCA. while responses mediated by cGMP activity are apparently enhanced by UDCA.

Effects of bile acids on fluid secretion, mucosal permeability and mucosal integrity in perfused intestine

When an *in vivo* intestinal perfusion technique was employed in rabbits, deoxycholic acid and chenodeoxycholic acid (5 mM/l; 1.25 ml/min) increased fluid secretion and mucosal permeability and caused mucosal damage, while ursodeoxycholic acid (5 mM/l; 1.25 ml/min) had no effect.

Esophageal mucosa

When rabbits were prepared with esophageal cannulas and perfused with taurochenodeoxycholic acid (TCDCA), ursodeoxycholic acid (TUDCA) and taurodeoxycholic acid (TDCA), TCDCA (1-5 mM) and TDCA (1-5 mM) produced more esophageal mucosal damage than TUDCA (1-20 mM).

B. Liver

Rats

Hepatic lipids

Rats were orally administered 15 mg/kg/day of chenodeoxycholic acid (CDCA) or 10 mg/kg/day of ursodeoxycholic acid (UDCA) for 2 weeks; a group of untreated rats served as controls. Synthesis of hepatic lipids was estimated by measuring incorporation of [1-^{14}C]acetate into different lipidic fractions by thin-layer radiochromatography. CDCA and UDCA decreased hepatic cholesterol by 29% and 52%, respectively, and decreased hepatic triglycerides by 61% and 78%, respectively.

C. Pancreas

Mice

Pancreatic histopathology

Two groups of mice were injected (route and site of injection were not provided) with 0.1 and 0.2 mg/day of ursodeoxycholic acid (UDCA), respectively, for 7 days; a third group with 0.2 mg/day of UDCA for 6 days and with both UDCA and 4 mg of alloxan (route and site of injection were not provided) on the 7th day; a fourth group with only 4 mg of alloxan on the 7th day. A fifth group of untreated mice served as controls. Pancreatic tissues were histopathologically examined after sacrifice on Day 8. UDCA produced cell proliferation and enlarged cisternae in β-cells and exocrine cells and hypertrophy of β-cells (incidences of lesions were not provided). Alloxan alone produced autophagic vacuoles in acinar cells and decreased numbers of β-cells. There were minimal pancreatic histopathological lesions in animals treated with both UDCA and alloxan.

Rabbits

Pancreatic secretion

Rabbits were surgically implanted with cannulas in the pancreatic and bile ducts, intraduodenally infused (0.4 mol/min/100 g) with either deoxycholate (DC), chenodeoxycholate (CDC), cholate (C), tauroursodeoxycholate (TUDC) or ursodeoxycholate (UDC) for 30 min, and intraduodenally infused at a rate of 0.8 mol/min/100 g for an additional 30 min. UDC produced increased pancreatic secretory volume (165%; % of control) and HCO_3- secretion (204%). None of the other bile acids had an effect on these pancreatic parameters.

D. Kidney

Rats

Urine volume and ionic content

Two groups of food and water deprived rats were orally administered 464 and 681 mg/kg of ursodeoxycholic acid, respectively; a control group received the vehicle. There were no treatment-related effects on urine volume and sodium, potassium and chloride levels in urine.

E. Central Nervous System

Electrically-induced convulsions

Two groups of mice were orally administered 464 and 681 mg/kg of ursodeoxycholic acid, respectively; a control group received the vehicle. There were no treatment-related effects on electrically-induced convulsions (30 Hz, 10 mA, 20 msec pulses for 0.6 sec). A positive control (pentobarbital, 20 mg/kg, p.o.) inhibited electrically-induced convulsions in all animals tested.

Pentetrazol-induced convulsions

Two groups of mice were orally administered 464 and 681 mg/kg of ursodeoxycholic acid, respectively; a control group received the vehicle. There were no treatment-related effects on pentetrazol-induced (110 mg/kg, s.c.) convulsions.

In summary, i.v. infusion of ursodeoxycholic acid (UDCA) in rats increased bile flow, bile acid levels, and biliary transport maximum (BSP T_m) of sulfobromophthalein. I.v. administration of UDCA in dogs increased bile flow. I.v. administration of UDCA in rabbits increased bile volume and HCO_3^- concentration. Since cholestasis is a major problem in PBC, any UDCA-induced increase in bile flow, bile acid levels and biliary transport maximum should be beneficial.

When bile ducts of rats were experimentally drained and obstructed, and the mice were intravenously infused (35 μmol/100 g) with either taurocholate (TC), taurochenodeoxycholate (TCDC) or tauroursodeoxycholate (TUDC); increases of hepatic and serum alkaline phosphatase were associated with retention of TC and TCDC, but not TUDC. The cholestasis in PBC is usually associated with elevation of alkaline phosphatase. Thus, treatment of PBC with UDCA, which is rapidly absorbed and conjugated in the liver with taurine, should alleviate the elevated alkaline phosphatase indirectly by reversing cholestasis.

ABSORPTION, DISTRIBUTION, METABOLISM & EXCRETION (ADME):

1. Absorption:

Rats

1. Pharmacokinetics of intravenously administered [■C]ursodeoxycholic acid (UDCA) in males after dietary administration for 3 weeks (Biochimica et Biophysica Acta 665:299-305, 1981; reprint provided by sponsor).

Animals: Male Sprague-Dawley rats (mean body weight of 175 g; ages were not provided).

Methods: Three groups of rats were fed standard diet (Group A, n=20), standard diet containing 5 mg/kg/day of UDCA (Group B, n=16) and standard diet containing 20 mg/kg/day of UDCA (Group C, n=16) for 3 weeks. After 3 weeks on the diets, one-half of the animals in each group were anesthetized with pentobarbital (5 mg/kg). Catheters were inserted into the bile duct and a carotid artery. Rats were intravenously administered [^{14}C]UDCA (2 μCi, 20 μg) via a saphenous vein in 500 μl of 0.1M NaOH. Blood samples were obtained via the carotid artery at 0, 2, 5, 10, 15, 20, 60, 90 and 120 min after injection. Simultaneously, bile samples were obtained every 5 min for the first 30 min after injection and at 40, 50, 60, 90 and 120 min after injection. Radioactivity was measured in a liquid scintillation counter.

Results: As shown in the following figure (from Vol. 7/page 268 of sponsor's submission), plasma clearance of radioactivity in Group A (controls) was biphasic with approximate half-lives of 2 and 30 min, respectively. Comparable values were obtained in both UDCA-treated groups. (More detailed pharmacokinetic data were not provided.)

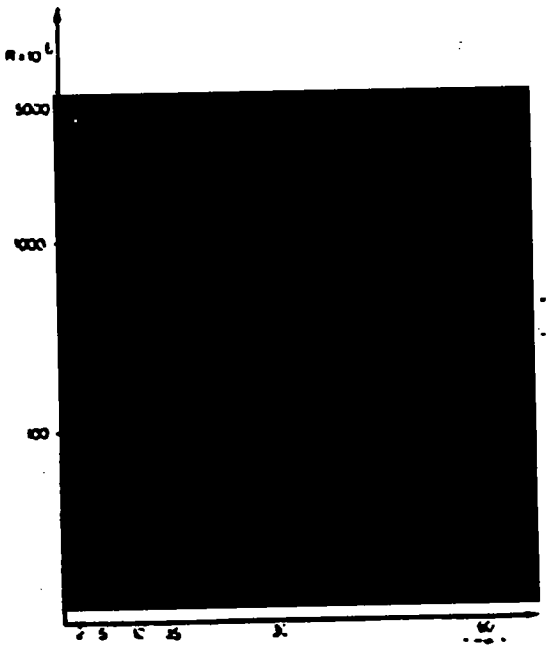


Fig. 1. Kinetics of [^{14}C]UDCA plasma disappearance after intravenous injection in controls. Comparable values were obtained in both UDCA-treated groups. Results were expressed as the fraction of dose: R = dpm/100 μl plasma/dpm dose.

2. Pharmacokinetics of ursodeoxycholic acid (UDCA)-24-[redacted]C after oral administration in non-lactating and lactating females (Hiroshima J. Med. Sci. 27, 1978; reprint provided by sponsor).

Animals: Non-lactating female (160-200 g; ages were not provided) and lactating female (250-300 g; ages were not provided) Wistar rats.

Methods: Three non-lactating females and three lactating females were orally administered 30 mg/kg of the sodium salt of UDCA-24-[redacted]C (1.0 μCi/mg); vehicle was water; dosing volume was not provided. Blood samples were obtained at 0.5, 1, 2, 4, 6, 8, 24, 72 and 168 h after dosing; site of blood withdrawal was not provided. Radioactivity was determined in a [redacted]

Results: As shown in the following table (from Vol. 7/page 280 of sponsor's submission), peak blood levels of radioactivity occurred within 30 min in both groups and rapidly decreased. Radioactivity was not detectable at 168 h after dosing.

Table 1. Blood level of radioactivity after a single oral administration of ursodeoxycholic acid-24-[redacted]C in female rats (30 mg/kg).

Time (hr)	Radioactive concentration (μg equivalent of UDC*/ml)	
	Female rats	Lactating rats
0.5	0.93±0.32**	1.45±0.55
1	0.40±0.13	0.55±0.09
2	0.40±0.23	0.42±0.11
4	0.40±0.06	0.37±0.11
6	0.31±0.03	0.25±0.05
8	0.28±0.03	0.28±0.08
24	0.08±0.02	0.15±0.02
72	0.12±0.04	0.12±0.03
168	ND***	

*UDC: ursodeoxycholic acid.
**Each value represents the mean and standard error of 3 animals.
***ND: not detected.

3. Absorption of orally administered ursodeoxycholic acid (UDCA)-24-[redacted]C (Hiroshima J. Med. Sci. 26, 1977; reprint provided by sponsor).

Animals: Male Wistar rats (180-220 g; ages were not provided).

Methods: Six groups of 24 rats each were orally administered 4, 10, 30, 60, and 200 mg/kg of UDCA-24-[redacted]C (26.6 μCi/μmol), respectively. Dosing concentrations varied from 20 to 2,500 mg%. Subgroups of 3 rats each were sacrificed at 5, 10, 15, 30, 45, 60, 90 and 120 min after dosing, respectively. Radioactivity of intestinal contents was measured with a [redacted]

Results: As shown in the following table (from Vol. 7/page 243 of sponsor's submission), 70%-90% of the radioactivity of orally administered doses of UDCA-24-[redacted]C (4 to 200 mg/kg) was absorbed into the intestinal tract over 120 min after dosing.

Table 1. Intestinal absorption of ursodeoxycholic acid-24-[redacted]C

Dose (mg/kg)	Concentration (μg)	Absorption (% of dose)							
	Time (min)	5	20	35	50	85	60	90	120
4	20	13.25 ± 2.07	19.14 ± 0.61	26.25 ± 2.07	41.35 ± 3.42	53.56 ± 3.58	63.41 ± 3.93	78.37 ± 1.49	85.64 ± 1.38
10	50	9.80 ± 1.31	15.64 ± 2.84	21.63 ± 2.18	35.37 ± 1.70	46.07 ± 1.04	55.57 ± 0.84	71.78 ± 1.60	79.31 ± 0.84
30	150	10.94 ± 3.98	20.87 ± 6.74	40.22 ± 5.67	54.20 ± 4.61	61.28 ± 3.75	69.22 ± 2.88	79.17 ± 1.48	84.75 ± 0.93
60	300	7.25 ± 3.87	12.01 ± 1.13	15.97 ± 0.71	26.32 ± 2.89	37.21 ± 0.94	46.87 ± 2.19	63.64 ± 0.37	72.40 ± 1.65
150	750	7.68 ± 2.75	14.17 ± 3.26	21.60 ± 3.57	34.17 ± 3.68	42.72 ± 4.22	54.62 ± 2.01	71.22 ± 1.32	78.63 ± 0.62
300	1,500	10.57 ± 1.16	14.96 ± 0.67	23.63 ± 0.11	33.21 ± 0.77	41.38 ± 0.89	49.99 ± 0.76	64.53 ± 0.48	74.63 ± 0.53

value represents the mean and standard error of 3 male rats.

Monkeys

Absorption of ursodeoxycholic acid (UDCA)-24-[redacted]C after oral administration (Hiroshima J. Med. Sci. 26, 1977; reprint provided by sponsor).

Animals: Male (6.6-7.9 kg; ages were not provided) rhesus monkeys.

Methods: Three males were orally administered 30 mg/kg of UDCA-24-^{14}C (20.6 mCi/mmol); vehicle was water; dosing volume was not provided. Blood samples were obtained at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72 and 168 h after dosing; site of blood withdrawal was not provided. Radioactivity was determined in a [redacted]

Results: As shown in the following table (from Vol. 7/page 301 of sponsor's submission), peak blood levels of radioactivity occurred at 30 min in both whole blood and plasma, and slowly decreased, being relatively low at 168 h after dosing.

Table 1. Blood and plasma levels of radioactivity after oral administration of ursodeoxycholic acid-24-[redacted]C in rhesus monkey (30 mg/kg)

Time (hr)	Radioactive concentration (μg equivalent of UDC/ml)							
	No. 1		No.2		No.3		Mean ± S E	
	Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma
0.25	[redacted]						11.29 ± 10.87	18.08 ± 17.30
0.5							19.03 ± 14.44	32.53 ± 23.98
1							14.89 ± 10.53	24.42 ± 16.82
2							5.80 ± 2.60	10.68 ± 4.91
4							5.46 ± 1.86	9.68 ± 3.77
8							6.29 ± 1.04	10.74 ± 2.32
12							3.78 ± 0.40	6.16 ± 0.76
24							1.75 ± 0.22	2.77 ± 0.41
48							0.64 ± 0.06	1.00 ± 0.12
72							0.47 ± 0.08	0.78 ± 0.16
168							0.17 ± 0.03	0.27 ± 0.05

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As shown in the following figure (from Vol. 7/page 302 of sponsor's submission), plasma clearance of radioactivity was biphasic with approximate half-lives of 6.3 and 64.2 h, respectively.

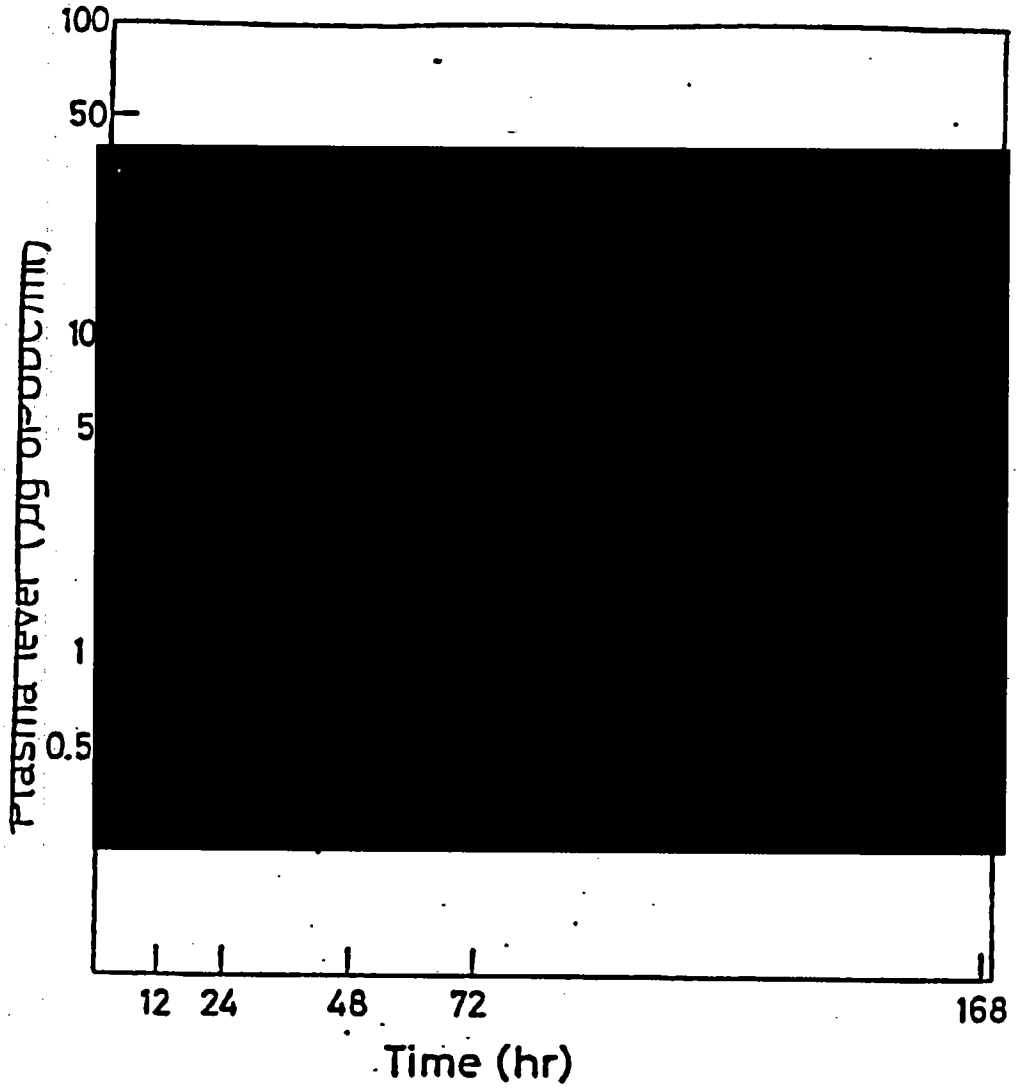

Fig. 3. Plasma level of radioactivity after oral administration of ursodeoxycholic acid-24-[redacted]C in rhesus monkey (30 mg/kg)

UDC represents ursodeoxycholic acid.
Each point represents the mean of three animals.