Effect of Ursodeoxycholic Acid Administration in Patients with Primary Hypercholesterolaemia

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Abstract

Objective: A high plasma cholesterol level is a major predisposing factor for coronary artery disease, and new treatments are currently under consideration. Supported by the close relationship between cholesterol and bile acid metabolism, recent studies have reported a hypocholesterolaemic effect of the bile acid ursodeoxycholic acid (UDCA) in patients with primary biliary cirrhosis but, unfortunately, no data are available in primary hypercholesterolaemia. We performed this study to evaluate the effects of oral administration of UDCA on serum lipoprotein patterns in patients with primary hypercholesterolaemia.

Design and Setting: A double-blind, placebo-controlled, crossover study with a 4-week washout period carried out at an outpatient clinic at a university hospital.

Study Participants: Twelve individuals with a total serum cholesterol level >5.17 mmol/L.

Intervention: Patients were assigned to receive UDCA (8 to 10 mg/kg/day) or placebo for 28 days. They then crossed over to receive the other treatment after a 4-week washout period.

Main Outcome Measures and Results: Serum total, low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL) cholesterol and apoprotein A1 and B100 were determined before and after 28-day UDCA and placebo administration. After UDCA administration, the mean (±SD) total serum cholesterol level decreased significantly from 6.37 ± 1.01 mmol/L to 6.06 ± 0.97 mmol/L (F = 5.7, p = 0.041); no significant differences from baseline were observed in LDL, HDL, VLDL cholesterol, apoprotein A1 and B100. No significant changes in serum lipid parameters occurred after the placebo period. When compared with placebo, the UDCA-induced decrease in total serum cholesterol levels was statistically significant (F = 5.5, p = 0.043).

Conclusion: This study shows that UDCA reduces total serum cholesterol levels in patients with mild to moderate hypercholesterolaemia. This effect suggests that the administration of UDCA may improve cholesterol metabolism in these individuals.
Hypercholesterolaemia is a major risk factor for atherosclerosis and coronary heart disease,[1] and new treatments for the management of this condition are currently under consideration.

The interaction between cholesterol and bile acid metabolism is well known.[2] The liver plays a major role in cholesterol metabolism,[3] and hepatic bile acid synthesis and biliary cholesterol excretion represent the major routes for cholesterol transformation and elimination.

It has been recently observed that the administration of ursodeoxycholic acid (UDCA), the 7-beta epimer of the primary bile acid chenodeoxycholic acid, decreases plasma total and low density lipoprotein (LDL) cholesterol levels in patients with primary biliary cirrhosis.[4]

UDCA has been successfully used for years as a dissolving agent for cholesterol gallstones,[3] and the effect of this bile acid on hepatic cholesterol metabolism has been extensively investigated.[2,6,7] Moreover, experimental studies have shown that UDCA can activate hepatic receptor-mediated LDL uptake.[8]

Nevertheless, to our knowledge, no definitive data concerning the effects of UDCA in primary hypercholesterolaemia are currently available. Therefore, the purpose of this study was to evaluate the effects of UDCA on serum total, LDL, high density lipoprotein (HDL), and very low density lipoprotein (VLDL) cholesterol, apoprotein A1 and B100 levels in primary hypercholesterolaemia.

**Patients and Methods**

**Participants**

Twelve individuals were recruited from consecutive patients attending the outpatient clinic of this department. All the patients had routine clinical, laboratory and instrumental work-up. The primary selection criteria were a serum cholesterol level >5.17 mmol/L[9] and age between 25 and 70 years.

Patients having diseases associated with secondary hypercholesterolaemia were excluded. In particular, alcohol abuse, renal or liver dysfunction, poorly controlled endocrine disorders and intra- or extrahepatic biliary obstruction were exclusion criteria. Patients taking lipid-influencing drugs during the month before the evaluation, as well as those previously treated with specific lipid-lowering agents, were also excluded.[9]

Selected participants were characterised as follows: five males, seven females; mean age ± standard deviation (SD): 54.3 ± 6.3 years, range: 41 to 66 years; mean total serum cholesterol level on admission to the study (±SD): 6.84 ± 0.92 mmol/L, range: 5.20 to 8.28 mmol/L.

**Methods**

The study protocol was as follows:

A double-blind crossover study design was used to compare UDCA treatment with placebo. UDCA (Deursil RR, Sanofi-Winthrop SpA, Milan, Italy) 8 to 10 mg/kg/day, in the form of a controlled-release capsule, was administered as a single dose after dinner. The capsules containing placebo were also administered as a single dose after dinner.

The dose of UDCA was chosen according to Bachrach’s and Hofmann’s guidelines for the treatment of cholesterol gallstones,[5] further confirmed by Johnston and Hofmann[10] and Hofmann.[11]

All patients underwent a 1-month preliminary run-in period and were placed on a standard weight-maintenance balanced diet, consisting of 17% proteins, 53% carbohydrates, 30% lipids. The average daily intake of cholesterol and fibre was 230mg and 22.6g, respectively. The same diet was continued for the entire duration of the study, and the adherence to diet was monitored by obtaining dietary histories.

After the run-in period, all participants underwent a 12-week experimental period in which they received each of the two consecutive treatments (UDCA-placebo or placebo-UDCA) for 4 weeks separated by a 4-week washout period. The participants were randomised to the treatment sequences on the basis of a computer-generated randomisation list: six participants were assigned to UDCA during the first period and placebo during the second, while the other six participants followed the reverse treatment order.