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The effects of ursodeoxycholic acid alone and ursodeoxycholic acid plus low-dose acetylsalicylic acid on radiolucent gallstones

Nonopak safra taşlan üzerine ursodeoksikolik asid ile ursodeoksikolik asid ve düşük doz aspirin kombinasyonunun etkileri

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Background/aims: *Mucin, a high molecular weight glycoprotein secreted by the gallbladder and biliary duct epithelium, is a pronucleating agent in experimental and human gallstone disease. Blockage of mucin release with aspirin inhibits the formation of primary gallstones in animal models. The aim of this study was to compare the effects of ursodeoxycholic acid alone and plus low-dose aspirin on dissolution of solitary or multiple gallstones.* ***Methods:*** *There were three treatment groups comprising 43 patients with cholesterol gallstones: Group I (n=16, 13 females, three males) was givenursodeoxycholic acid (15 mg. kg. day) alone and Group II (n=14, 12 females, two males) was treated with aspirin (100 mglday) in addition to ursodeoxycholic acid cholic. Group III was a control group of 13 cases (11 females, two males) who were monitored without medical treatment. Stone dissolution rates were evaluated sonographically in all patients at three month intervals during the treatment period.* ***Results:*** *After 12 months of treatment, stone dissolution was found in six (37.5%) of the patients in Group I and six (42.8%) of the patients in Group II. The difference in both treatment groups was significant compared to controls ($p<0.05$) but there was no significant difference between the two treatment groups ($p>0.05$). Of the cases in whom dissolution was achieved, all patients had multiple gallstones except for one with a solitary stone in Group I. Gallstones were not dissolved of any subject of group III.* ***Conclusions:*** *The results showed that ursodeoxycholic acid cholic therapy is more effective in the dissolution of multiple gallstones than of solitary ones. Combination with aspirin did not potentiate the efficacy of ursodeoxycholic acid cholic.*

Key words: Gallstone dissolution, ursodeoxycholic acid, aspirin

Amaç: *Musin, safra kesesi ve safra yollarından salgılanan yüksek molekül ağırlıklı bir glikoproteindir. Deney hayvanlarında ve insanlarda oluşan safra taşı patogenezinden sorumlu tutulan bir ajandır. Hayvan modellerinde aspirinle musin salınımının baskılanması safra taşı oluşumunu inhibe etmektedir. Çalışmanın amacı; multipl ve soliter safra taşlarının çözünürlüğü üzerine ursodeoksikolik asit ile ursodeoksikolik asit ve düşük doz aspirin kombinasyonunun etkilerini araştırmaktır.* ***Yöntem:*** *Çalışmada nonopak safra taşı (çapı <2cm) saptanan 43 hasta randomize olarak üç gruba ayrıldı. Grup I (n=16; 13 kadın, 3 erkek)'deki hastalara tek basına 15mg/kg/gün ursodeoksikolik asit, Grup II (n=14; 12 kadın, 2 erkek)'deki hastalara 15mg/kglgün ursodeoksikolik asit ve 100 mglgün aspirin verildi. Grup III (n=13;ll kadın, 2 erkek)'deki hastalar tedavi almaksızın kontrol grubu olarak takip edildi. Tüm hastalarda safra taşı çözünürlüğü 3 aylık aralar ile ultrasonografik olarak değerlendirildi.* ***Bulgular:*** *12 aylık tedavinin sonunda komplet taş çözünürlüğü grup I'deki hastaların 6'sında (37.5%), grup Il'deki hastaların 6'sında (%42.8) sağlandı. Çözünen taşların biri haricinde tümü multipl taş idi. Grup IU'deki olgularda taş çözünürlüğü gözlenmedi.* ***Sonuçlar:*** *Taş çözünürlülüğü yönünden ursodeoksikolik asit tedavisinin, soliter taşlara oranla, multipil taslar üzerine daha etkili olduğunu gösterdi. Düşük doz aspirinin tedaviye eklenmesi taş çözünürlüğü hızını artırmamaktadır.*

Anahtar kelimeler: Safra taşı, ursodeoxycholic acid, aspirin

INTRODUCTION

Gallstones are often identified incidentally during evaluation of other disorders. The prevalence of gallstone disease in western industrialized nations is about 10-15% (1, 2). Recurrent episodes of upper abdominal pain related to gallstones are the most common indication for the treatment of gallstones (2, 3). Cholecystectomy is the standard and definitive treatment for symptomatic gallbladder stones and can be performed regardless of the type, number, and size of the stones. However, if a patient with gallbladder stones refuses surgery or is unsuitable for a general anesthetic, alternatives may need to be considered (2, 4).

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Identifying the type of gallstone has clinical importance because only cholesterol gallstones are amenable to dissolution with oral bile acid therapy (2,5). Candidates for treatment with bile salts should have noncalcified cholesterol gallstones and a patent cystic duct (2,6). The best bile acid therapy currently available is probably ursodeoxycholicacid (UDCA), which is well tolerated (4,7). It is a bile salt that both reduces the secretion of cholesterol into bile and increases cholesterol solubility (2, 3, 6).

Prostaglandins are thought to be potent inhibitors of gallbladder motility. Impaired gallbladder motility in patients with gallstone disease is corrected by short-term oral aspirin even in low dosage (2, 8, 9). High doses of aspirin reduce the incidence of gallstones in the dog model, perhaps because they inhibit the synthesis of mucus in the gallbladder, but aspirin has had only variable success in other animal models and humans (9, 10).

The aim of this study was to determine the effects of UDCA-alone and UDCA plus aspirin on stone dissolution in patients with solitary and multiple radiolucent gallbladder stones.

MATERIALS AND METHODS

Between 2000 and 2002, 55 patients (46 female, nine male; age range: 25-69 [mean:47.1±12] years with asymptomatic or mildly symptomatic cholesterol gallstones (less than 2 cm in diameter) were enrolled in this randomized study.

Evaluation for each subject included a complete history and physical examination, complete blood count, serum cholesterol, triglycerides, aminotransferases, total bilirubin and alkaline phosphatase, serum amylase, abdominal x-rays, and abdominal ultrasound.

All gallstone patients were candidates for oral bile acid therapy (radiolucent gallstones, less than 2 cm in diameter, good gallbladder emptying, patent cystic duct, mild symptoms, and no evidence of acute cholecystitis). Fourty-four patients with two or more gallbladder stones were defined as having multiple stones whereas the remaining 11 patients had solitary stones. There was no history of recent pancreatitis, cholangitis or biliary colic in any of the patients. Patients with a history of systemic disease, current pregnancy or lactation and alcohol or medication use were excluded.

Sonographic studies were performed by the same investigator (I.A.). Stone dissolution was measured using a real-time ultrasound scanner (Toshiba SSA-270A, Japan, with a 3.75-mHz curved transducer).

All patients gave informed consent to participate in the study. They were randomized into three groups: Group I (n=20) received UDCA alone (15 mg. kg. day, Ursofalk, Falk PharmaGmbH, Germany); Group II (n=20) received aspirin (100 mg/day) plus UDCA (15 mg. kg. day) and Group III the control group (n=15) was monitored without medical treatment.

The physical examination and blood samples were repeated in each patient in three-months intervals during the treatment period. In addition, gallbladder motility and gallstone dissolution rates were evaluated by ultrasonography in all patients at the third, sixth, ninth and twelfth months.

Patients were not allowed to take any other drugs affecting biliary lipids or cholesterol biosynthesis and were excluded from the study if they exhibited any abnormality of gallbladder, bile duct or pancreatic function as determined by x-ray or ultrasonography. The treatments were discontinued at the sixth month if stone dissolution was not achieved.

Results are presented as mean values± standard deviation (X±SD). For statistical comparison of the three groups before and after treatment, one-way ANOVA variance analysis was used. Within group analysis for comparison before and after the treatment was performed with paired-student's t test. Stone dissolution rates were compared with chi-square test. The difference was considered statistically significant if the P value was less than 0.05.

RESULTS

Two patients in Group I, and four patients in Group II were excluded from the study due to non-attendance with the treatments. In addition, two patients in Group I were excluded due to severe biliary colic in one and acute edematous pancreatitis in one, while two patients in Group II and two patients in Group III underwent urgent laparoscopic cholecystectomy and were therefore also excluded. The final analysis was performed with 16 patients (13 female, there male) from the UDCA group, 14 patients (12 female, two male) from UDCA plus aspirin group and 13 patients (11 female, 2 male) from the control group. There were no statistically significant differences

Table *1.* Demographic and clinical features of groups before treatment*

Parameters	UDCA *(n=16)*	UDCA&Aspirin *(n=14)*	Control *(n=13)*
Mean age	44.2±14	46.7±12	49.0±8
Gender(F/M)	13/3	12/2	11/2
BMI (kg/m^2)	30.7±6	28.6+3	3l.3±5
Glucose (mg/dL)	89.7±15	88.5+18	96.2+7
Cholesterol (mg/dL)	170.4±39	196.0±33	177.0+26
HDL-Cholesterol (mg/dL)	46.7±13	50.8+17	43.0+9
LDL-Cholesterol (mg/dL)	89.7.0±35	124.3+48	108.4±15
Triglyceride (mg/dL)	153.6±82	202.7+86	145.7+81
Solitary stone	5	3	2
Multiple stone	11	11	11

*Results are expressed as mean±SD.
BMI: body mass index

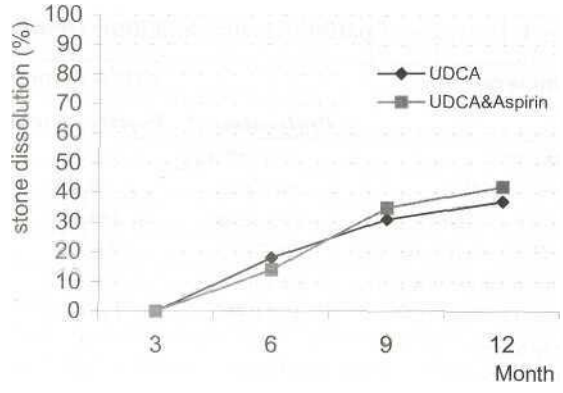

Figure 1. Stone dissolution rates with time in both treatment groups

between groups regarding demographic, clinical and laboratory data on admission. The patient characteristics are presented in (Table 1).

At the end of the treatment period of 12 months, complete stone clearance was achieved in six (37.5%) of the patients in Group I and in six (42.8%) of the patients in Group II. Gallstones were not dissolved in any subject in Group III. The difference was statistically significant compared to controls in both treatment groups ($p<0.05$) but there was no difference between the two groups ($p>0.05$). Of the 12 cases in whom dissolution was achieved, all had multiple gallstones except for one in Group I. Solitary gallstones did not disappear in any subject treated with a UDCA and aspirin combination. The gallstone dissolution rate at 12 months was higher for UDCA plus aspirin than treatment with UDCA-alone. Characteristics of the patients at the end of treatment are given in Figure 1 and Table 2.

Laboratory tests including serum alkaline phosphatase, cholesterol, aspartate and alanine aminotransferase were measured at three-months intervals, and results of these tests showed no change during the treatment periods in all groups (Table 3).

Ursodeoxycholic acid and aspirin were generally tolerated quite well. The drugs did not cause any severe gastrointestinal or other side effects. Both regimens showed no significant difference in terms of side effects or drop-out rate. There was a remarkable decrease in symptoms in patients in whom stone dissolution was achieved. In patients with partial stone dissolution, the therapy was continued beyond the study period.

Table 2. Features of patients with and without stone dissolution*

Parameters	**UDCA alone**				**UDCA &Aspirin**			
	Solitary (n=5)		***Multiple (n=ll)***		***Solitary (n=3)***		***Multiple (n=ll)***	
	**** (+)***	***SD (-) n=4***	***SD (+) n=5***	***SD (-) n=6***	***SD (+) n=0***	***SD (-) n=3***	***SD (+)***	***SD (-) 71=5***
Age (mean)	35	47.4±6	35.7±4	46.8±9		44.8±2	39.4+5	45.8±4
Gender (F/M)	*11-*	4/-	4/1	4/2		3/-	5/1	4/1
BMI (kg/m^2)	32	30	28.5	29.5		29.5	27	29
SS» (mm)	7	13.8	-	-		14.2	-	-

*Results are expressed as mean±SD
'"SD: stone dissolution; BMI: body mass index; SS«: average stone size

Table 3. Features of patients before and after treatment*

Parameters	UDCA alone			UDCA & Aspirin		
	Pretreatment	*Posttreatment*		*Pretreatment*	*Posttreatment*	
BMI (kg/m^2)	30.7±6	29.2±6	NS	27.4±3	26.7± 7	NS
Glucose (mg/dL)	89.7±15	94±5	NS	99±20	96±18	NS
Cholesterol (mg/dL)	170.4±39	184±42	NS	186+30	188±50	NS
HDL- Cholesterol (mg/dL)	46.7±13	48.2±8	NS	53.5±17	60.7±9.2	NS
LDL- Cholesterol (mg/dL)	89.7.0±35	101±52	NS	104±51	108±38	NS
Triglyceride (mg/dL)	153.6±82	148± 59	NS	157±73	176±48	NS
Solitary stone	5	4	NS	3	3	NS
Multiple stone	11	6	NS	11	5	NS

*Results are expressed as mean±SD.

BMI: body mass index

NS: not significant

DISCUSSION

The treatment of gallstones without surgery has long been a goal of medical therapy. Both oral bile acid dissolution therapy and extracorporeal shock-wave lithotripsy are successful only in patients whose gallstones are composed predominantly of cholesterol (11). The therapeutic success of the medicial dissolution of gallstones depends on patient selection, dosage of bile acid therapy and duration of therapy (4, 11-13).

Therapy with bile salts is suitable for only the minority of patients with symptomatic cholesterol gallstones who refuse or who are at high risk for surgery (2, 4, 11). The bile acids chenodeoxycholic acid and UDCA were the first widely available alternatives to surgery (2, 4, 14).

In this study, complete gallstone dissolution rates of 37.5% with UDCA and 42.8% with combination therapy was achieved at 12 months. The stone dissolution rate was higher in patients with multiple stones compared to those with solitary stones but this difference was not statistically significant. A combination of UDCA with aspirin did not improve complete gallstone dissolution rate. Stone dissolution rates were increased with longer treatment periods. The only solitary stone dissolved with treatment was 7 mm in diameter and none of the solitary stones larger than 1 cm was dissolved. In both treatment groups, the use of UDCA was found to be associated with a reduced incidence of biliary pain.

Based on a simple correlation with the gallstone dissolution rate, small size, radiolucency of gallstone and good gallbladder emptying have been listed as indication criteria for UDCA therapy. Size rather than number of stones is the primary determinant of the dissolution rate (11, 15, 16). Gallstones smaller than 5 mm show a better dissolution rate at almost 79% than those exceeding 5 mm (15) and stones larger than 10mm have a success rate of approximately only one third (4, 11, 15, 16). With stones larger than 15-20 mm in diameter, the dissolution rate is extremely slow (4, 17).

Ursodeoxycholic acid completely dissolved the stones in 37% of all patients (13). Jazrawi et al (18) reported a complete stone dissolution rate of 78% with UDCA treatment at the end of six months, whereas Schoenfield et al (19) reported a success rate of 50% at the end of 24 months. On the other hand, Bazzoli et al (20) achieved a stone dissolution rate of as low as 13% at the end of six months. The wide variation in the reported response rates can be attributed to differences in patient selection, doses of bile acid therapy, treatment duration and the diagnostic techniques used to document complete stone dissolution (13).

Mucin, a high molecular weight glycoprotein secreted by the gallbladder and biliary duct epithelium, are pronucleating agents in experimental and human gallstone disease. Blockage of mucin release with aspirin inhibits the formation of primary gallstones in animal models (10, 21-23).

There are some other studies which contradict the above findings and which found that aspirin does not seem to influence mucin production, biliary cholesterol, lipid composition and the formation of cholesterol crystals in gallstone disease patients (24, 25). Animal studies have also shown that the

addition of aspirin to a lithogenic diet does not reduce the incidence of cholelithiasis (26). In another study, low-dose aspirin (100 mg/day) was not able to reduce gallstone recurrence rate after successful extracorporeal Shockwave lithotripsy (9). Aspirin was reported to reduce biliary glycoprotein concentration in higher doses (1200 mg/day) but without a significant improvement in the incidence of gallstones (27). Moreover, Pazzi et al (28) suggested that chronic treatment with nonsteroidal-antiinflammatory drugs (NSAIDs) did not inhibit the formation of primary cholesterol gallstones. Our findings showed that the addition of aspirin to treatment did not change the rate of stone dissolution.

In previous studies different results have been reported about the effects of UDCA alone or in combination with other drugs on gallstone dissolution. The combination of UDCA with chenodeoxycholic acid therapy enhances the biliary levels of UDCA (29). Zuin et al (30) obtained a gallstone dissolution rate of 83% with a UDCA plus chenodeoxycholic acid combination in 12 months, whereas Petroni et al (31) found the rate to be 30% with the same combination in 24 months. Moreover, Tazuma et al (32) found a 70% stone dissolution rate of multiple stones and 25% of solitary stones at the end of 12 months in patients treated with UDCA. In the same study, combination with simvastatin was not proven to be superior to UDCA treatment alone. The stone dissolution rate was lower in this study than that reported by Tazuma et al. The differences between these studies may be due to the characteristics of patients recrvited. As in previous studies, we failed to show superiority of combination therapy over UDCA treatment alone on dissolution of multiple or solitary stones.

In conclusion, the present authors found higher gallstone dissolution rates in patients with multiple stones compared to those with solitary stones, as in previous studies. The administration of combined UDCA and low-dose aspirin therapy is not likely to provide an effective combination. Younger patient age and longer treatment periods appear to increase the chance of successful treatment and long-term medical treatment with bile salts may help to reduce gallstone-related complications and need for surgery, especially in multiple cholesterol gallstones, in which both the risk of complication and the benefit of therapy is greatest.

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