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Ursodeoxycholic Acid for the Treatment of Cholesterol Gallstones

M. K. Zaater

Health Radiation Research Dept., National Center for Radiation Research and Technology (NCRRT), P. O. Box; 29 Nasr City, Cairo, Egypt. Internal Medicine and Nephrology Unit.

E- Mail: mahmoudzaater@Gmail.com

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ABSTRACT

Cholesterol is the principal constituent of more than three quarters of gallstones. Pure cholesterol crystals are quite soft, and protein contributes importantly to the strength of cholesterol stones. The risk of gallstones does not correlate with total serum cholesterol levels, but it does correlate with decreased high-density lipoprotein cholesterol and increased triglyceride levels. At least 10 percent of adults have gallstones where female: male ratio of about 2:1 in the younger age groups with increasing prevalence with age. Nine patients with gallstones (6 females and 3 males) were included in the study. Patients were treated with ursodeoxycholic acids tablets in two oral doses, one after breakfast, and the other after dinner for 9 months. Ultrasound examination was repeated every 3 months. Re-examination by abdominal ultrasonegraphy revealed that gallstone 1cm or less in diameter disappeared within 6 months, and the largest stone 3.06 cm in diameter disappeared within 9 months.

Key words: Ursodeoxycholic acid, Cholesterol gallstones.

INTRODUCTION

Gallstones are composed mainly of cholesterol, bilirubin, and calcium salts, with smaller amounts of protein and other materials [(1)]. Activation of liver X receptor sensitizes mice to gallbladder cholesterol crystallization [(2)].

Cholesterol is the principal constituent of more than three quarters of gallstones, many of these stones contain more than 80 percent cholesterol. Cholesterol stones often contain alternating layers of cholesterol crystals and

mucine glycoprotein [3]. Pure cholesterol crystals are quite soft, and protein contributes importantly to the strength of cholesterol stones. Cholesterol is virtually insoluble in aqueous solution, but in bile it is soluble by association with bile salts [4].

Lithogenic bile is most often the result of increased biliary cholesterol output. The biliary output of cholesterol increases with age [5], as well as estrogen treatment also reduces the synthesis of bile acid in women [6]. The risk of gallstones does not correlate with total serum cholesterol levels, but it does correlate with decreased high-density lipoprotein cholesterol and increased triglyceride levels. The bile is supersaturated in the morning before breakfast because most total-body bile acids are sequestered in the gallbladder and the output of bile acid in hepatic bile is consequently reduced more than the output of cholesterol [7].

Bile from patients with gallstones forms cholesterol crystals more quickly than bile from patients without gallstones [8].

Gallbladder sludge i.e. thickened gallbladder mucoprotein with tiny entrapped cholesterol crystals is thought to be the usual precursor of gallstones[9].

At least 10 percent of adults have gallstones. The prevalence varies with age, sex, and ethnic group. Ultrasound surveys show a female: male ratio of about 2:1 in the younger age groups and an increasing prevalence with age; after the age of 60 about 10 to 15 percent of men and 20 to 40 percent of women have gallstones [10]. In a recent ultrasound survey in Denmark, a large population was re-examined at five-year intervals. In each five-year period, new gallstones formed in about 3 percent of the population over the age of 40 [11].

METHODS

We studied consecutive adult patients complaining of recurrent episodes of right upper quadrant or epigastric pain, with or without fever and vomiting. In addition to physical examination, the following tests were carried out:

1- CBC and ESR.

2- Liver enzymes.

3- Lipid profile.

4- Abdominal ultrasound and plain x-ray of abdomen.

Inclusion criteria:

1- Patient who has symptoms suggestive of gallstone disease due to single radiolucent stone (proved by ultrasound examination and x-ray).

2-Thin gall-bladder wall by ultrasound examination.

3- No signs of infection.

Exclusion criteria:

1- Patient with diabetes mellitus.

2- Patient with cardiovascular disease.

3- Patient with symptoms and ultrasound examination suggestive of impacted stone, (dilated common bail-duct), elevation of gamma GT or, alkaline phosphatase.

Nine patients met our inclusion/exclusion criteria, 6 females and 3 male.

Patients were given ursodeoxycholic acid as oral 250mg tablets in two doses ,one after breakfast ,and another after dinner, for 9 month. Ultrasound examination was repeated every 3 month and at the end of the study by the same machine and the same operator in the same center.

Patients with dyslipidemia were treated with gemfibrozil 600mg tablets.

RESULTS:

Abdominal ultrasonography of our patients revealed single floating radiolucent cholesterol stone ranging between 0.8 cm and 3.06 cm in diameter.

Their lipid profile revealed increase in triglyceride 250- 360 mg/dl, with accepted range of serum cholesterol less than 200 mg/dl .and IDL-cholesterol less than 120 mg/dl.

All patients were non diabetic, had normal serum creatinine (equal or less than 1.0 mg/dl) and liver enzymes levels.

Gallstone 1cm or less in diameter had disappeared within 6 months, and the largest stone 3.06 cm in diameter had disappeared within 9 month.

An example of those patients that participated in the study:

Mr. Emad M. 35 year old male came to the clinic complaining of recurrent right upper quadrant pain, with recurrent episodes of vomiting. The

abdominal ultrasonography and X-ray revealed a single gallstone 3.06 cm in diameter (fig 1). Patient was treated as the protocol with Ursodeoxycholic Acid 250mg twice daily and gemfibrozil 600mg orally for 3 months.

The abdominal ultrasonography after 3 months revealed a single gallstone 1.32 cm in diameter,(fig. 2).Treatment taken for another 3 months. Re-examination by abdominal ultrasonography revealed no gallstone, (fig 3).

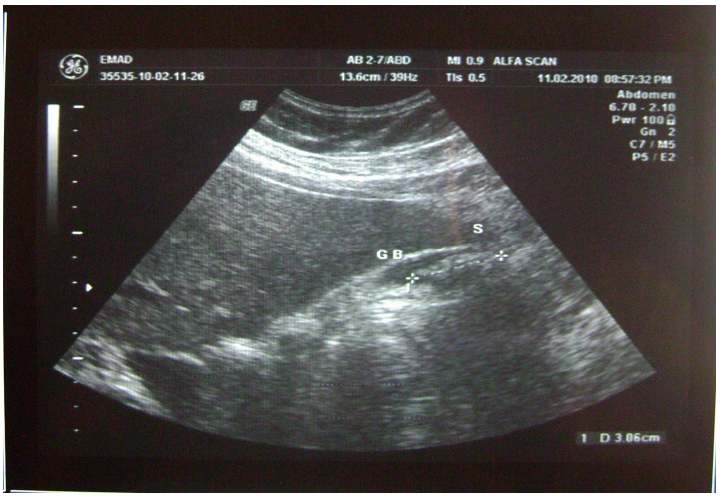

Fig. 1: revealed GB stone 3.06 Cm

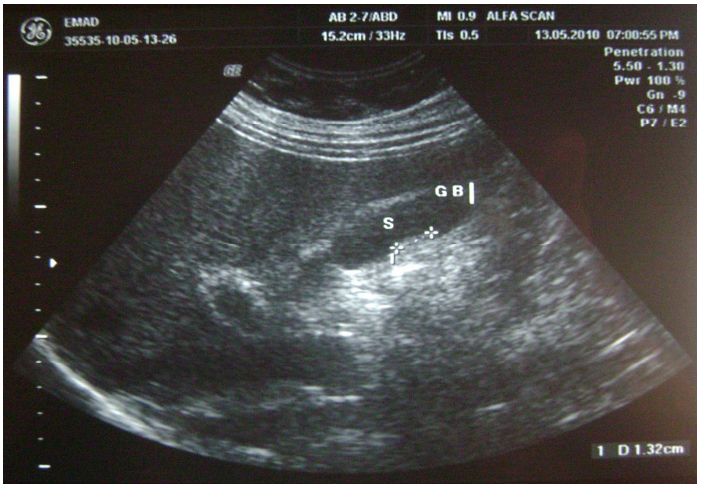

Fig 2 Revealed GB stone 1.32 cm

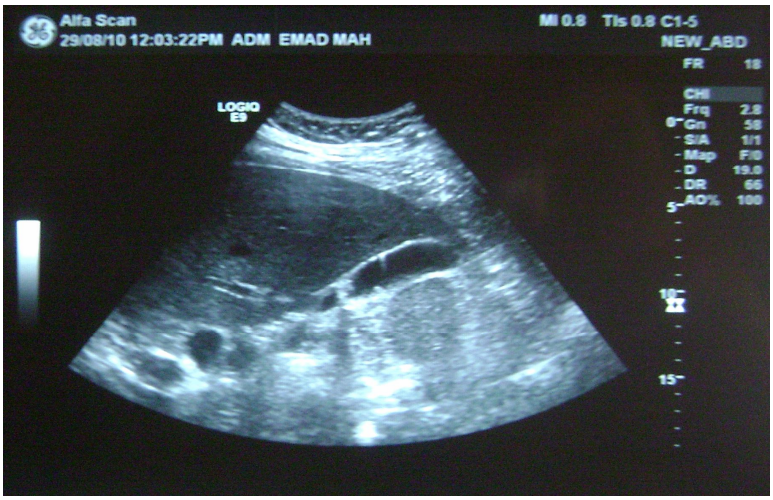

Fig 3 Revealed no GB stone

DISCUSSION

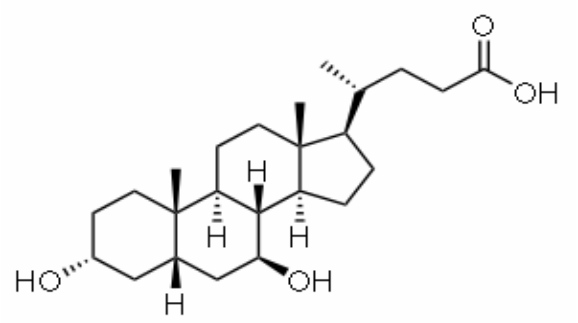

Fig. 4. Ursodeoxycholic acid

Ursodeoxycholic acid is the principal bile acid in bears, normally constitutes only 1 to 2 percent of bile acid in humans [(12)]. When ursodeoxycholic acid is given orally, it is absorbed, transported to the liver, and undergoes rapid and extensive biotransformation, predominantly involving conjugation with glycine and taurine. Tauroursodeoxycholate undergoes significant deconjugation and reconjugation during its enterohepatic recycling. The proportion of lithocholate in bile remained unchanged. Fasting serum conjugated ursodeoxycholate concentration positively correlated with the ursodeoxycholate dose, and the increased proportion of ursodeoxycholate was accompanied by substantial decreases in the endogenous bile acids. The shift toward a more hydrophilic bile acid pool is greater and potentially more

favourable with tauroursodeoxycholate, and this is because of the reduced intestinal biotransformation of tauroursodeoxycholate. The glycine/taurine ratio of the biliary bile acid pool decreased from 1.9 at baseline, to 1.1[13].

However ursodeoxycholic acid is converted to more hydrophilic bile acid, chendeoxycholic and lithocholic acid. The conjugated bile acid tauroursodeoxycholic acid (TUDCA) is more effective therapeutic agent. TUDCA have stronger cytoprotective than ursodeoxycholic acid against liver injury induced by hydrophobic bile acid. Biliary ursodeoxycholic acid enrichment and shift in the hydrophobic/hydrophilic composition of the TUDCA. Enrich the biliary bile acid pool with hydrophilic bile acid induce a choleresis. Ursodeoxycholic acid inhibits the intestinal uptake of cholic acid lead to increased loss of cholic acid into the colon, with the consequence of increased formation of the secondery bile acid, deoxycholic acid. TUDCA lead to significant reduction in the biliary composition of the hydrophobic bile acid and chendeoxycholic acid [13]. It suppresses hepatic synthesis and secretion of cholesterol inhibits intestinal absorption of cholesterol, but it does not inhibit the synthesis of endogenous bile acids [14]. In addition, it also solubilizes cholesterol in micelles and causes dispersion of cholesterol as liquid crystals in aqueous media. Overall, it makes the bile conducive to cholesterol stones dissolution. It occurs naturally in bile, where it has an important role in controlling the concentration of cholesterol in the blood .It causes a competitive blockade of bile acid reabsorption in terminal ileum, causes cholesterol desaturation in bile without raising serum cholesterol levels, which prolongs the nucleation time of gallbladder bile by shifting cholesterol from vesicles to micelles [15]. It is prescribed as an alternative to surgery in the treatment of gallstones. It acts by reducing levels of cholesterol in the bile.

Adverse Effects

The most commonly reported adverse effect of ursodeoxycholic acid is weight gain, which averages approximately 2.3 kg during the first 1 to 2 years [16].This increase in weight is not progressive. Some patients have reported thinning of the hair, although this symptom is not well described in the literature and is relatively uncommon. Loose stools have been reported infrequently [17].

Drug Interactions.

There are a few drugs that have important interactions with ursodeoxycholic acid; these include clofibrate, cholestyramine, and other

cholesterol-binding or bile acid–binding sequestrants. Estrogens may increase biliary cholesterol levels, whereas charcoal and some antacids may bind bile acids. The dose of ursodeoxycholic acid does not have to be adjusted for renal or other hepatic diseases [17].

CONCLUSION

Ursodeoxycholic acid can be used in patient to treat pure cholesterol gallstone as an alternative to surgery, with no or few adverse effect as weight gain, or/and thinning of the hair.

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مجلة البحوث الإشعاعية
والعلوم التطبيقية
مجلد ٤ عدد ٤(أ) ص ص ١٠٦٥ – ١٠٧٣ (٢٠١١)

استخدام عقار حامض اورسو دي اوكسي كولين في علاج حصوات الكوليستيرول المرارية

محمود كامل زعتر

قسم البحوث الصحية الإشعاعية ، المركز القومي لبحوث و تكنولوجيا الإشعاع ، ص. ب. ٢٩ مدينة نصر ، القاهرة ، مصر

الكوليستيرول هو العنصر الاساسي المكون لحوالي ثلاث أرباع الحصوات المرارية ،كرستالات الكوليستورول النقيه لينه ويساهم البروتين مساهمه فعاله فى صلابة حصوات الكولسترول. الإصابة بحصوات الكوليسترول لا علاقة لها بالمستوى العام للكوليسترول بالدم بل بمستوى الدهون المنخفضة الكثافة ومستوى الدهون الثلاثية. على الأقل ١٠% من البالغين مصابون بالحصوات المرارية، نسبة الإصابة فى الذ كور ضعف الإصابة فى الإناث فى المراحل العمرية المتوسطة ،وتزداد هذه النسبة مع التقدم فى العمر. فى هذ ا البحث تم علاج ٩ مرضى مصابون بالحصوات المرارية بعقار الأرثو دى أوكسى كوليك الحمضى بمعدل جرعتين يوميا لمدة تسع أشهر. تم عمل فحص بالموجات فوق الصوتية كل ثلاثة أشهر. عند إعادة الفحص بالموجات فوق الصوتية تبين أن الحصوات التى قطرها ١سم أو اقل قد إختفت تماما فى فتره زمنيه قدرها ستة أشهر، كما إختفت حصوة من المرارة قطرها ٣ سم بعد ٩ أشهر .