

Gallbladder stones: Oral dissolution therapy

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ABSTRACT: Chenodiol is noninvasive, safe and moderately expensive. Because of diarrhea, the need for aminotransferase monitoring, the long duration of therapy required, and the minority of patients who are appropriate candidates, it has had limited use. Ursodiol is generally preferred because it has minimal side effects. Patients with increased surgical risk, mild to moderate symptoms, and gallstones which are either floatable with oral radiopaque contrast media or radiolucent by computed tomography scan in a nonobstructed gallbladder are appropriate candidates for oral bile acid therapy. Silent stones should not be treated under most circumstances. *Can J Gastroenterol* 1990;4(9):621-623

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La dissolution des calculs biliaires par voie orale

RESUME: L'acide chénodésoxycholique (Chénodiol) est non invasif, sûr et de coût modéré. Vu les diarrhées fréquentes qu'il provoque, la nécessité de vérifier les transaminases, la durée prolongée du traitement requis, et le nombre réduit de candidats appropriés, son utilité a été limitée. L'acide ursodésoxycholique (Ursodiol) lui est généralement préféré à cause de ses effets indésirables minimes. Les patients présentant une contre-indication majeure à la chirurgie, des symptômes faibles à modérés, des calculs bien visibles dans une vésicule qui s'opacifie ou des lithiases radiotransparentes cholestéroliques, et une vésicule fonctionnelle objectivée par cholécystographie, sont les candidats au traitement par les acides biliaires per os. Dans la majorité des circonstances, les calculs asymptomatiques ne devraient pas être traités.

BOTH CHENODEOXYCHOLIC ACID (chenodiol) and ursodeoxycholic acid (ursodiol) are approved for use in the United States by the Federal Food and Drug Administration. Either alone or in combination, these bile acids are effective in slowly dissolving gallstones which are almost pure cholesterol. Both bile acids decrease hepatic biliary cholesterol secretion resulting in micellar desaturation in cholesterol. Ursodiol

also dissolves biliary cholesterol by liquid crystal formation.

CHENODIOL

Predictable cholesterol desaturation of bile requires ingestion of 12 to 15 mg/kg/day of chenodiol in nonobese patients (1). In obesity, biliary cholesterol secretion is increased in proportion to excess body weight and 18 to 20 mg/kg/day may be required to achieve

micellar desaturation in these patients. This may be difficult to tolerate because of dose-related side effects; however, ingestion of a dosage insufficient to desaturate bile is of no value.

Most patients initially develop at least transient intermittent increased stool frequency with or without cramping when a fully therapeutic dosage is ingested (2). The diarrhea is often episodic, eg, occurring once every week or two, and usually decreases after several weeks to months if the patient continues to titrate the dose as tolerated. The diarrhea effect is dose-related and immediately resolves when the dose is decreased sufficiently. The mechanism of the diarrhea is inhibition of normal water and electrolyte absorption by the colon. No long term consequence of this diarrhea has been documented.

Aminotransferase elevations (usually less than threefold) occur commonly and are also dose-related (2). Like the diarrhea, this side effect also usually returns to normal during the first few months of treatment. Higher enzyme levels are rare, but chenodiol should be discontinued if these occur. An acceptably prudent monitoring regimen would be to assess aminotransferase levels monthly for three months and then at six, 12, 18 and 24 months. In the National Cooperative Gallstone Study in the United States (2), elevation of serum total cholesterol 10 mg/dL greater than in the placebo group was observed, and this elevation was predominantly in the low density lipoprotein fraction. Dietary restriction

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Figure 1) Stones which layer out (float) in orally administered radiopaque contrast material demonstrated on decubitus film

of cholesterol and saturated fat might minimize this slight tendency for elevation of cholesterol and may enhance efficacy, although these benefits have not been proven. Serum total cholesterol levels should be assessed before and six months after initiating therapy.

Because of the potential for diarrhea, an initial daily dose of 500 mg should be prescribed for the first week or two. This can then be increased by 250 mg at weekly intervals until a therapeutic dose is achieved, usually 750 to 1250 mg daily depending on body weight. Taking most of the chenodiol before bed with a stimulus to gallbladder contraction (fat or protein), may enhance its cholesterol desaturating effect (3). Chenodiol costs about US \$1000 annually, and complete stone dissolution for most patients requires one to two years of treatment.

URSODIOL

This bile acid is at least as effective as chenodiol in decreasing cholesterol saturation of bile, but can also solubilize cholesterol by inducing liquid crystal formation (4,5). Its effective dosage is 8 to 10 mg/kg daily in nonobese patients. The only well documented side effect of ursodiol is diarrhea, but this is substantially less frequent than with chenodiol. Depending on how it is defined, about 5% of patients may get diarrhea; occasionally this is sufficient to prevent treatment with this agent. It seems like-

ly that the mechanism for this diarrhea is similar to that associated with chenodiol, and that tolerance might also develop. The development of stone surface calcification during ursodiol has been described but is infrequent and has not been proven to be more common than that during chenodiol therapy.

A before bed dose with this bile acid may also optimize efficacy, although this has not been thoroughly established. Bioavailability of a large single dose is of some concern. A compromise involves administration of up to 750 mg before bed and any additional ursodiol with breakfast. Intraluminal solubilization and absorption of ursodiol is enhanced by bile, and administration with a stimulus to gallbladder contraction seems empirically appropriate.

Ursodiol has largely replaced chenodiol because of infrequent diarrhea and the absence of aminotransferase elevation. Indeed, ursodiol has been shown to decrease hepatic enzyme levels in several chronic, especially cholestatic, liver diseases. The major disadvantage of ursodiol is its expense of about US \$2 per 300 mg capsule. Most patients require two or three capsules a day, leading to a cost of at least US \$1500 per year for most patients.

A combination of chenodiol and ursodiol has been proposed both to decrease expense and possibly to increase efficacy (6). Some evidence suggests that the combination may be more effective than either bile acid alone during the first six months, but the differences are minor after 12 months of treatment. It would be of interest to compare the usefulness of the combination versus ursodiol alone after extracorporeal shock wave lithotripsy to see if complete dissolution of the fragments at six months would be greater. The effect of either bile acid on gallbladder motility and on biliary symptoms before stone dissolution is achieved remains controversial.

PATIENT SELECTION

Bile acid therapy induces secretion of bile with a reduced cholesterol content and, in sufficient doses, produces a milieu which can resolubilize the crystalline cholesterol in stones. The stone

cholesterol, however, must be accessible; even a very thin layer of calcium bilirubinate or calcium carbonate will prevent dissolution. Many stones which cannot be detected on abdominal plain film will have calcification demonstrable by computed tomography scan. It is unreasonable to expect bile acid therapy to dissolve this calcified stone material (7). Since all patients with gallstones developed them partly because their gallbladder did not spontaneously evacuate them when they were microscopic or sandlike, there is no reason to imagine that fine residual debris will be predictably and completely emptied at a later date.

Consequently, if complete gallbladder clearance is the objective, only stones which are virtually pure cholesterol can be expected to have a high rate of complete disappearance with oral bile acid therapy. Stones which float (layer out) at oral cholecystography usually have a very high cholesterol content and are the most appropriate candidates for oral dissolution therapy if symptoms are sufficiently infrequent (Figure 1). Most floatable stones are 10 mm or less in diameter. Pigment stones, which comprise about 20% of gallstones, are also almost always small, usually less than 5 mm in diameter. Pigment stones, however, do not float and they are often very irregular in contour. On computed tomography scan, black bilirubin polymer pigment stones in the gallbladder can usually be seen to be calcified if 3 mm slices are obtained without contrast. Note that after oral cholecystography, it may take at least a week before sufficient contrast has been cleared from the gallbladder so that stone calcification is not masked by contrast when computed tomography scan is performed. Considering the cost of a 12 month trial of oral bile acid therapy, a computed tomography scan would be a cost effective patient selection parameter if the stones do not float on oral cholecystography (7).

Obviously, the cystic duct must be patent for oral bile acid therapy to be a consideration. This is usually best demonstrated by oral cholecystography because of the additional information

obtained, but an isotope biliary scan or convincing evidence of gallbladder emptying by ultrasonography are acceptable alternative methods. Occasionally cystic duct patency will have been demonstrated by endoscopic retrograde cholangiopancreatography. If so, even patients who have had an endoscopic papillotomy may have the potential to respond to oral bile acid therapy if they have appropriate stones.

GALLSTONE RECURRENCE

Data on gallstone recurrence has been limited by the thoroughness with which complete dissolution has been documented. At least two thorough ultrasonograms provide the most convincing baseline. The recurrence data available are almost all relevant to oral bile acid therapy, which, reflects a highly selected subpopulation of patients with gallstones who have very high cholesterol content stones. These usually small stones may have been present for only a few months or years and may be associated with very little chronic gallbladder inflammation or scarring. In these selected patients, stones recur in about 10% of patients per year for the first four or five years (8). Some studies suggest that the greatest risk is in the first year (9). If the patient continues to have all of the prerequisites for stone formation, it is

logical to expect that stones will form again rapidly after therapy is discontinued. It makes equal intuitive sense that if stones have not recurred within five years, the patient may no longer be in an active stone-forming phase. Patients who develop stones during a period of rapid weight loss or estrogen therapy may be less likely to develop recurrence when these predisposing factors are no longer present. Patients who have had solitary stones are less likely to develop stone recurrence than those with multiple stones (10). The risk of stone recurrence appears to be 40 to 60% after five years following oral bile acid therapy (11).

Although a stone-free gallbladder is usually considered the goal of oral dissolution therapy, the more specific objective of gallstone treatment is the elimination of biliary symptoms. If stones recur but remain asymptomatic, one might consider treatment to have been successful. The frequency with which recurrent stones have become symptomatic has varied widely, but they often remain silent at least for several years. There is general agreement that silent stones do not require treatment except under rare circumstances.

Encouraging progress in understanding the pathogenesis of cholesterol gallstones has evolved during

the past five years. Abnormally rapid nucleation of cholesterol in bile has been demonstrated in most patients with cholesterol gallstones and characterization of nucleating factors as well as antinucleating factors is well under way (12). Cholesterol gallstone formation can be prevented by administration of nonsteroidal anti-inflammatory agents in the prairie dog model system, and preliminary data suggest that this approach may have potential in humans (12). Cholesterol synthesis inhibitors induce some desaturation of cholesterol in bile; further work in this area may also provide a practical pharmacologic approach to stone prevention (13).

The search continues for a novel bile acid which will desaturate bile in cholesterol and resist hepatic or bacterial degradation yet be actively transported by the ileum and liver. A useful agent must have no acute or chronic serious side effects such as hepatotoxicity or detrimental effects on lipid metabolism. Alternatively, the cost of ursodiol may be markedly reduced as patent protection runs its course and manufacturing methods are refined. Development of a safe, economical, well tolerated prophylactic agent would greatly enhance the usefulness of all nonsurgical treatments for gallstones which are evolving.

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