New Drugs

Gall stone dissolving agents

IAN A D BOUCHIER

During the decade in which the medical dissolution of gall stones has become feasible several drugs have been introduced but only the two listed in the British National Formulary have been intensively evaluated and shown to be effective—chenodeoxycholic acid and the closely allied ursodeoxycholic acid. The dissolution of gall stones was last reviewed in the "BMJ" in 1976, at which stage experience with chenodeoxycholic acid was limited. Since then the indications and potential for this bile acid in treating gall stones have become better understood, and data on the newly introduced ursodeoxycholic acid are being evaluated. Cholesterol, but not pigment, gall stones are amenable to oral dissolution treatment. This review will cover firstly, chenodeoxycholic acid, secondly, ursodeoxycholic acid, then a comparison of the two drugs, an assessment of the place of medical dissolution in the management of gall stones, and, finally, the dissolution of stones in the common bile duct.

Chenodeoxycholic acid

Chenodeoxycholic acid (Chendol, Chenofalk) is available as 125 mg or 250 mg capsules. The recommended dose is 10-15 mg/kg/day, but it may also be given as a fixed dose of 1000 mg daily. It is administered in divided doses with meals. Some authorities recommend that for better action the bile acid should be given as a single dose in the evening. The action of chenodeoxycholic acid is to reduce the cholesterol content of bile, thereby diminishing the biliary cholesterol saturation and enabling unsaturated bile which enters the gall bladder to dissolve cholesterol gall stones. It remains uncertain precisely how biliary unsaturation is achieved, but it may be consequent on one or more of the following mechanisms: inhibition of hepatic cholesterol synthesis, inhibition of cholesterol absorption, or an acute effect on biliary lipid secretion by the hepatocyte. The oral administration of chenodeoxycholic acid also expands the total bile salt pool, but this is thought to be less important.

There are few contraindications to its use. It should not be given to patients who are icteric or who have diarrhoea, and women who may become pregnant should not receive the drug, but if there is a particular indication in such women adequate precautions should be taken against becoming pregnant. Dissolution treatment may be used only if symptoms are mild because of the time it takes for the stones to disappear. The drug should not be used in acute gall bladder disease, and most authors agree that it is best avoided in managing common bile duct stones as they have potentially serious complications.

Several extensive clinical studies have largely clarified the

circumstances under which the maximum benefit might be expected from chenodeoxycholic acid. The gall bladder must be functional to enable the progress of gall stone dissolution to be followed radiologically and to ensure that the stones are exposed to the dissolving effects of the unsaturated hepatic bile. The recently published American National Cooperative Gallstone Study, however, observed that some patients whose gall bladder could not be visualised developed radiological function during treatment. Thus the occurrence of a radiologically non-visualised gall bladder during treatment is not necessarily a reason to discontinue treatment. Only radiolucent stones are treated. Most authors advise against treating gall stones that are radio-opaque and therefore contain calcium, but the American study, surprisingly, reported that some radio-opaque stones could be dissolved completely. These were stones with "slight" as compared with "prominent" calcification. Dissolution is more effective in thin patients and those with stones under 15 mm in diameter. The larger the stones the longer it takes for them to dissolve.

There is no general agreement over the efficacy of chenodeoxycholic acid, and it is particularly unfortunate that the National Cooperative Gallstone Study selected a dose that was almost certainly suboptimal for most of the patients included in the trial. The results of this study showed complete dissolution in only 13.5% of patients and a partial response in 25%. Dissolution rates in other studies have varied from 10 to 90%. There are several reasons why results are apparently so different. Complete dissolution of the gall stone usually takes between 12 and 24 months, and many studies have been reported prematurely to include a large number of patients with partially dissolved gall stones. The assumption is that these stones will go on to complete dissolution but this is not necessarily so, and a final outcome of partially dissolved stones is of little benefit to the patient. The only result that is meaningful is the complete disappearance of gall stones.

Then, too, there have been different entry criteria to the various studies, with some including all patients referred for dissolution treatment, others that analysed only patients who had had at least six months of treatment, and yet others that evaluated patients who had completed at least 24 months of treatment. Maton and his colleagues reported the final outcome in 125 patients with radiolucent gall stones who had had a full course of treatment and observed an overall efficiency of 38%, which was comparable with other reports in which an adequate dose of chenodeoxycholic acid had been administered. The complete dissolution rate rose to 76% when a group of patients were treated who showed selection criteria ideal for dissolution of the gall stone, such as radiolucent stones of under 15 mm in functioning gall bladders, the administration of optimal doses of the bile acid (>13 mg/kg/day) for at least 12 months, and the demonstration that with this dose the bile had become unsaturated with cholesterol. Apart from reducing the size of cholesterol gall stones there is some evidence that some of the symptoms that accompany gall stone disease, such as right upper quadrant discomfort and dyspepsia, are improved.

University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY

IAN A D BOUCHIER, MD, FRCP, professor of medicine

Few drugs have been studied for toxic effects with as much care and detail. Chenodeoxycholic acid seems to be perfectly safe when used for up to three years. The only troublesome side effect is diarrhoea, which becomes more frequent as the dose is increased but may be alleviated by reducing the dose. Once normal bowel habit has been restored it is often possible to return to a larger dose without a concomitant increase in stool frequency. A rise in concentrations of serum aminotransferases and other liver derived enzymes will be observed but is not clinically important, and chenodeoxycholic acid does not induce any permanent histological change in the liver. Patients who achieve a reduction in the size of their gall stones do not have an increased tendency to develop choledocholithiasis, nor is there any evidence that bile acid treatment is accompanied by malignant changes in the biliary system.

Ursodeoxycholic acid (Destolit)

Ursodeoxycholic acid is the 7 β -hydroxy epimer of chenodeoxycholic acid, and it too is capable of dissolving cholesterol gall stones. The bile acid is available as 150 mg tablets, and the recommended dose is 8-10 mg/kg bodyweight/day (600 mg daily), divided into two doses taken after the evening meal and one other meal. The indications, contraindications, and precautions are similar to those of chenodeoxycholic acid. The mode of action of ursodeoxycholic acid has yet to be clarified. It reduces the content of cholesterol in the bile, and this may be due to either a reduction in hepatic cholesterol synthesis or reduced absorption of cholesterol, or a combination of both. There has, however, been much less experience with ursodeoxycholic acid, which has been evaluated in detail only since 1975. It seems to be more efficient than chenodeoxycholic acid in achieving biliary cholesterol unsaturation, which suggests that smaller doses than chenodeoxycholic acid may be possible. Our studies indicate that a daily dose of 600 mg is as effective as 1000 mg to dissolve gall stones. A possible disadvantage may be a tendency to induce calcification of gall stones.

The outstanding attraction of this bile acid is its freedom from unwanted side effects. Diarrhoea is virtually unknown, no appreciable changes occur in biochemical tests of liver function, and liver histology is unaltered. In contrast to chenodeoxycholic acid there is only a slight increase in the hepatotoxic secondary bile acid, lithocholic acid.

Selecting a bile acid for treatment

It remains to be established that one bile acid is preferable to the other for dissolving gall stones, but the evidence seems to favour ursodeoxycholic acid. Ursodeoxycholic acid causes less diarrhoea, is not hepatotoxic, and may be more potent, thereby enabling smaller doses to be used than chenodeoxycholic acid. Many gastroenterologists would regard ursodeoxycholic acid as the drug of first choice even though dissolution rates at least similar to chenodeoxycholic acid are achieved.

Policy decisions

SELECTING PATIENTS

No patient should start treatment without radiological or ultrasonographic evidence of gall stones. Bile acid treatment should not be started in patients with undefined dyspepsia. Only cholesterol gall stones respond to treatment, and best results are given when the patient is thin and there are small radiolucent gall stones in a functioning gall bladder. Obesity is not a bar to treatment and may even be an indication when the surgeon rejects a very overweight patient as being at greater risk at operation. Such obese patients may require proportionately larger doses of the bile acid (18-20 mg chenodeoxycholic

acid/kg bodyweight/day). We do not know for certain what proportion of all patients with gall stones are suitable for oral dissolution treatment. It may well be under 30% once we exclude those patients who have calcified stones, a non-functioning gall bladder, severe symptoms or complications, and, in the case of women, are of child bearing age. Furthermore, some 14-20% of radiolucent gall stones are non-cholesterol in composition. Patients for whom the bile acid might be recommended include those who are judged to be at increased risk at operation, those who refuse an operation, or those who wish to delay gall bladder surgery. The presence of gall stones is not, in itself, an indication for treatment for only about 13% of silent gall stones cause symptoms, and severe, life threatening complications are usually preceded by a period of moderate gall stone related complaints.

PREDICTING RESPONSE

When treatment has to be prolonged to be successful it is advantageous to determine as early as possible whether or not the gall stones are responding. There is only one practical method, the oral cholecystogram or, when appropriate skills are available, the ultrasonic scan. It is impractical to use the measurement of cholesterol saturation and bile acid content in the biliary drainage as an index of response. Monitoring the serum bile acid concentrations has been suggested, but more experience with this technique is required. The oral cholecystogram obtained after six months of treatment predicts in over 80% of patients what the outcome will be. Patients who show some response are likely to achieve complete dissolution, and treatment should be continued until two consecutive cholecystograms taken three months apart indicate a normal gall bladder, and this is usually achieved by 24 months. A successful outcome is unlikely if stones persist, even if partially dissolved, for over three years. Patients whose stones show no alteration after six months should be treated for a further six months, and if the repeat cholecystogram shows no response treatment should be discontinued.

It is not necessary to monitor liver function. Diarrhoea resulting from treatment with chenodeoxycholic acid is managed by reducing the dose. Calcified stones and a non-functioning gall bladder are reasons for stopping treatment, but drugs may be continued in the presence of light calcification.

RECURRENCE

One of the disappointments with dissolution treatment has been the frequency with which the gall stones recur once the bile acid has been discontinued. Recurrence is maximal in the first two years after stopping treatment and increases with time, probably to nearly 100% if the patients are followed up for long enough. There is no agreed way of managing patients once the stones have been dissolved. Intermittent treatment is valueless. Studies are in progress to determine the lowest dose of continuous treatment that will prevent stones from reforming, and the benefit of a high fibre diet is also being assessed. There is no information about the hazards of long term, full dose bile acid treatment, but at present this is the only established method of ensuring that the stones do not recur. A decision will have to be made in the case of each patient whether or not to continue full dose treatment indefinitely or whether to discontinue the drug and recommend cholecystectomy should gall stones return.

MEDICAL AGAINST SURGICAL TREATMENT

No clinical trials have been done to compare drug treatment with cholecystectomy and an adequate study is unlikely to be practical given the time scale required. The cost of dissolution treatment is about £400 a year, and to this must be added the

cost of doing at least two cholecystograms. It is more difficult to place a precise cost on a cholecystectomy if this includes the time off work during the postoperative and convalescent period. Properly prosecuted, a cholecystectomy is a curative operation with a mortality rate of under 1%; but the mortality rate may be above 5% when complications are present, and it is in just such conditions that dissolution treatment is inadvisable. Medical treatment is recommended for a selected group of patients; surgical treatment may be offered to virtually all patients, though there is an increased risk in some. The aged patient and those with medical disorders that carry an increased operative risk are the group to whom drugs might be offered.

Common bile duct stones

The growing skill with endoscopic retrograde cholangiography and sphincterotomy and the introduction of Dormia basket removal through the T-tube tract are tending to replace the *in situ* dissolution of retained common bile duct stones. If dissolution is contemplated the agent of choice is the medium chain fatty acid mono-octanoin (glyceryl-1-mono-octanoate) that is instilled continuously into the bile duct at 2-4 ml/h. Infusion at this rate reduces the frequency of adverse effects such as nausea, vomiting, abdominal pain, and diarrhoea. Mono-octanoin may be used only for cholesterol stones and is generally successful within one to three weeks.

Conclusions

The treatment of choice for gall stones remains cholecystectomy. At present radiological monitoring of patients under treatment is required, but there is no reason why, given adequate access to appropriate facilities, bile acid treatment should not be given by general practitioners. Unfortunately, the introduction of drugs to dissolve gall stones has been seen as a threat by many surgeons who have eschewed them as a therapeutic option. Medical dissolution should take its place with surgical inter-

vention in managing gall stone disease. Properly used in correctly selected patients, bile acid treatment has much to offer.

Bibliography

- Bouchier IAD. Gall stones. *Br Med J* 1976;ii:870-2.
The last time that this topic was reviewed in the *BMJ*.
- Bouchier IAD. The medical treatment of gallstones. *Annu Rev Med* 1980; 31:59-77.
A review of the pharmacology of chenodeoxycholic acid, the indications for its use, and side effects. Other agents that have an effect on the size of gall stones are evaluated, and there is a comprehensive list of references.
- Jarrett LN, Bell GD, Balfour TW, Knapp DR, Rose DH. Intraductal infusion of mono-octanoin: experience in 24 patients with retained common bile duct stones. *Lancet* 1981;i:68-70.
The value of mono-octanoin is assessed in treating common bile duct stones. The method is given of how the drug is administered, and the safety, side effects, and efficacy are evaluated.
- Maton PN, Iser JH, Reuben A, Saxton HM, Murphy GM, Dowling RH. Outcome of CDCA-treatment in 125 patients with radiolucent gallstones. Factors influencing efficacy, withdrawal, symptoms, and side-effects and post-dissolution recurrence. *Medicine* 1982;61:86-97.
This report documents six years' experience with chenodeoxycholic acid in over 100 patients. There is an excellent evaluation of factors that determine efficacy, on the basis of which a prediction has been made of those patients most likely to have a satisfactory outcome. These were put to the test in a prospective study. The paper includes data on the recurrence of gall stones after discontinuing treatment.
- National Cooperative Gallstone Study. Chenodial (chenodeoxycholic acid) for dissolution of gallstones. *Ann Intern Med* 1981;95:257-82.
The largest and most elaborate study of chenodeoxycholic acid treatment. There is a detailed review, on the basis of 916 patients who were studied, of the efficacy, prediction of dissolution, safety, serum lipids, liver histology, and overall assessment of chenodeoxycholic acid. Despite the use of inadequate doses of bile acid this paper repays detailed study.
- Tokyo Cooperative Gallstone Study Group. Efficacy and indication of ursodeoxycholic acid treatment for dissolving gallstones. *Gastroenterology* 1980;78:542-8.
This paper sets out recent Japanese experience with ursodeoxycholic acid. Although it may not be possible to extrapolate the doses used in this study to Western patients, the study gives an excellent account of the potential for this bile acid and includes analyses of bile, side effects, and a discussion on the mechanism of action.

On the grounds that shielding an infant's immature gastrointestinal tract from cows' milk for the early months of life is believed to protect the infant from developing an allergy, is there any evidence that a similarly immature respiratory tract should be shielded from other allergens such as pollen and house dust in so far as this is possible?

There is considerable controversy over the suggestion that allergy may be prevented by dietary manipulations. Atopic individuals sometimes have a temporary defect of immune function in early infancy, during which period they can become sensitised. Matthew *et al*¹ studied a group of infants born to allergic parents. Those mothers who had elected to breast feed were advised to follow a regimen including exclusive breast feeding from birth to 3 months and only selective weaning from 3 to 6 months. The mothers were also recommended to try to eliminate house dust mites and were selected only if they did not own pets. This treatment was compared with a non-treatment group of infants who were bottle fed, and their parents were given no advice on avoiding environmental allergens. When reviewed at 1 year, significantly more of the non-treatment group developed eczema compared with the treatment group. The predominant factor influencing this was assumed to be the breast feeding. Other investigations, however, have indicated that dietary manipulations in infancy have, if anything, only a small effect, and some have suggested that they merely postpone the development of allergy or have no effect whatsoever. I believe that the fundamental difference between the studies was that Matthew *et al*¹ used measures to avoid additional environmental inhaled allergens. Protection from common inhaled allergens may therefore be more important than avoidance of food allergens. This impression is supported by the observation that there is a variation in the month of birth among patients with sensitivities to allergens. More asthmatic children with an allergy to house dust mite are born in the months from

September to December, at a time when mite frequency is at its highest in household dust.² Recently, a group from Finland have estimated that the incidence of allergy to birch pollen might be reduced by 28% if susceptible children were not born in the two months before the pollen season.³ Thus the answer to the question is almost certainly "yes."—J O WARNER, consultant paediatrician, London.

- ¹ Matthew DJ, Taylor B, Norman AP, Turner MW, Soothill JF. Prevention of eczema. *Lancet* 1977;i:321.
² Warner JO, Price JF. House dust mite sensitivity in childhood asthma. *Arch Dis Child* 1978;53:710-4.
³ Bjorksten F, Suoniemi I, Koski V. Neonatal birch-pollen contact and subsequent allergy to birch-pollen. *Clin Allergy* 1980;10:585-91.

What is Mondor's disease, and how should it be treated?

Mondor's disease is thrombophlebitis of superficial veins of the breast. It is rare, usually affecting the thoracoepigastric vein,¹ which runs from the hypochondrium to the axilla. The vein becomes tender, and fibrosis around it produces a palpable cord that may groove the skin when the arm is raised. The condition resolves completely, usually in six to eight weeks, and requires no treatment,¹ though restriction of arm movement may be recommended.² Rarely it may affect the male breast.³ The cause is unknown (though some cases may be due to trauma), and the only complication is that a mistaken diagnosis of carcinoma may lead to unnecessary biopsy.—JAMES OWEN DRIFE, senior lecturer in obstetrics and gynaecology, Leicester.

- ¹ Haagensen CD. *Diseases of the breast*. 2nd ed. Philadelphia: Saunders, 1971:343.
² Rains AJH, Ritchie HD, eds. *Bailey and Love's short practice of surgery*. 17th ed. London: Lewis, 1977:642.
³ Oldfield MC. Mondor's disease: a superficial phlebitis of the breast. *Lancet* 1962; i:994-6.