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Ursodeoxycholic acid in chronic liver disease

J S de Caestecker, R P Jazrawi, M L Petroni, T C Northfield

Abstract

The hydrophilic bile acid ursodeoxycholic acid has recently been shown to reduce biochemical markers of both cholestasis and hepatocellular damage in patients with chronic liver diseases. The most compelling evidence available is for chronic cholestatic liver diseases, in particular primary biliary cirrhosis, primary sclerosing cholangitis, and cholestasis associated with cystic fibrosis. The effects may be less beneficial in patients with advanced liver disease from these conditions. Data from placebo controlled trials are now available in support of earlier uncontrolled observations, but it is not yet clear whether short term benefit results in an improvement in longterm prognosis. The mechanism of action of the compound seems to reside in its displacement of toxic hydrophobic bile acids from both the bile acid pool and hepatocellular membranes. There may be an independent effect on bile flow, which could be of particular importance in cystic fibrosis, and possibly an effect on the immune system. Ursodeoxycholic acid should now be regarded as occupying a central place in the medical management of chronic cholestatic liver diseases, in particular primary biliary cirrhosis, because it improves cholestasis and reduces hepatocellular damage and it is not toxic. Research should now be targeted on whether treatment with ursodeoxycholic acid, initiated early in cholestatic liver conditions, improves the long-term outcome.

The bile acid ursodeoxycholic acid occurs naturally in small quantities in human bile (<4% of total bile acids). It is formed by 7-β epimerisation of the primary bile acid chenodeoxycholic acid through the action of intestinal bacteria. It was first isolated earlier this century from the bile of the Chinese black bear, after which species it was named.[1] Nearly 40 years ago it was manufactured synthetically in Japan, finding use as a treatment for a wide range of liver diseases. Its popularity stemmed not from rigorous scientific study but from a longstanding tradition of the beneficial properties of black bear bile ('*Yutan*').[1] More general interest in the compound was aroused 15 years ago when Japanese investigators reported that ursodeoxycholic acid desaturated bile and dissolved cholesterol gall stones.[1,2]

Leuschner and colleagues were the first to report in an English language journal improvement in liver function tests in patients with liver disease.[3] As a chance finding, they observed this improvement in a group of patients with chronic liver disease who were receiving ursodeoxycholic acid to dissolve gall stones. This report stimulated interest in the compound as a treatment for a variety of adult and childhood liver disorders, principally those resulting in cholestasis. The result has been a large number of uncontrolled studies, with the preliminary results of controlled studies now beginning to emerge. This review attempts to place in perspective the role of ursodeoxycholic acid in the treatment of liver disease, with discussion of recent data on its mechanism of action. The aim will be to conclude what implications arise for current clinical practice and future research.

Clinical studies

PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis is an example of a disease in which two different processes may be injuring the liver.[4] One is the immunological injury to intrahepatic bile ducts by mechanisms which are still poorly understood.[5] Most drugs that have been evaluated for treatment of primary biliary cirrhosis have been used in an attempt either to influence this abnormal immunological response or to inhibit the fibrosis consequent on chronic inflammatory damage. Although some, such as colchicine, cyclosporin, and methotrexate seem promising and are still being evaluated, use of others such as penicillamine and prednisolone has now been abandoned.[5,6]

The second mechanism, possibly a consequence of the first, is the retention of hydrophobic endogenous bile acids, including chenodeoxycholic, deoxycholic, and lithocholic acids (see Figure). These are damaging to cellular membranes, such as the bile canalicular membrane[7] and may thus aggravate the cholestasis.[1,4] Fisher and Paradine were the first to report a beneficial effect of ursodeoxycholic acid in patients with primary biliary cirrhosis,[8] followed by Poupon and colleagues in a report published in the *Lancet* and attracting much interest.[9] The latter group observed in an open study improvement in both symptoms and serum enzyme markers of cholestasis with ursodeoxycholic acid given over a two year treatment period, with subsequent deterioration when it was discontinued. Several uncontrolled studies have confirmed these original observations,[10–14] but all have been small studies with fewer than 20 patients. Nevertheless, there has been a striking uniformity in these reports of improvement in symptoms and serum transaminases as well as alkaline phosphatase and γ glutamyltransferase. All enzyme levels were reported decreased to 30–70% of pretreatment values. Glutamine dehydrogenase, a hepatocyte mitochondrial enzyme and a specific indicator of hepatocyte damage, is also decreased.[15] Thus, serum enzyme markers of both cholestasis and hepatocellular damage are reduced on treatment.

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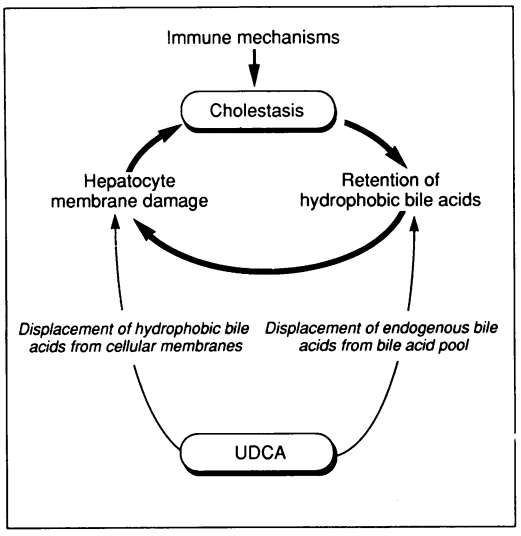

Putative pathophysiology of primary biliary cirrhosis and mechanisms of action of ursodeoxycholic acid (UDCA). Bold arrows indicate an increased effect, light arrows a decreased effect.

These encouraging results are now being confirmed in controlled studies,[15-21] including three large multicentre studies.[17 20 21] The results from four trials[15 16 18 21] giving sufficient information are summarised in the Table. These include the two which have appeared as full papers and two abstracts. Only in the two full papers[15 21] is sufficient information supplied to determine that the active and placebo groups are well matched (Table). Some of the reports are based on interim analysis at an interval of six months[17 20 21] and others are only short term studies, though one has given results after two years of treatment.[16] Although in some of the open studies symptoms were reported to improve during ursodeoxycholic acid treatment, several of the controlled studies have found that symptoms such as pruritus and fatigue, though reduced, are diminished to the same extent with ursodeoxycholic acid as with placebo.[15 17 21] The maximum reduction in serum biochemical parameters occurs during the first year of treatment.[16] Hadziyannis and colleagues found that, particularly in patients with stages III and IV of the disease, biochemical and symptomatic deterioration occurred during the second year of treatment.[16] This complements other uncontrolled observations that patients with late stage disease either respond poorly or may even deteriorate on ursodeoxycholic acid.[22 23] Serum IgM decreases during treatment,[15 19-21] hinting at an effect of ursodeoxycholic acid on the immune process, although no changes in antimitochondrial antibody titre have been observed in these reports. Finally, histological improvement in liver biopsy specimens has been reported in four studies, notably a reduction in inflammation, bile ductular proliferation, and epithelial cell proliferation (Table).[15 18 19 21]

OTHER CHOLESTATIC LIVER DISEASES

Ursodeoxycholic acid treatment has been tried in a variety of other liver conditions. Symptoms and serum enzyme markers of cholestasis and hepatocellular damage in primary sclerosing cholangitis have been shown to improve in both open[24 25] and controlled studies.[26] Inevitably, numbers have been small in these studies because the disease is rare. In the cholestatic liver disease associated with cystic fibrosis, average reductions in alanine transaminase of 60% and alkaline phosphatase of 47% were observed after six months of treatment with ursodeoxycholic acid in an open study.[27] This study also reported an improvement in nutritional state on treatment despite a lack of effect on steatorrhoea. The improvement in transaminases in this condition has been confirmed in a placebo controlled trial.[28] In patients undergoing surgery for obstructive jaundice, a randomised trial of ursodeoxycholic acid administration before surgery did not show any benefit in terms of endotoxaemia, renal failure, or postoperative morbidity and mortality.[29] A short term (three months) controlled trial in children suffering from a variety of cholestatic liver diseases was reported to benefit neither symptoms nor biochemical parameters.[30]

There are reports suggesting that ursodeoxycholic acid may be administered with benefit to children who have had biliary reconstructions

Summary of some controlled studies of ursodeoxycholic acid in primary biliary cirrhosis

Study	No of subjects*	Ursodeoxycholic acid dose (mg/kg/day)	Histological stage (No of subjects)	Time of analysis (months)	% change from baseine§ Alkaline phosphatase	Alanine transaminase	γ glutamyl-transferase	Bilirubin	Serum IgM	Histology
Leuschner *et al* (1989)[15]†	20	10	I (7)‡ II (10) III (3)	3	−55	−61	−73	-	−30%	Two deteriorated, six improved of 10 on ursodeoxycholic acid; four deteriorated, one improved of 10 on placebo
Hadziyannis *et al* (1989)[16]	50	10–15	All stages (no details)	6 12 18–24	−42 −42 −37	−37 −41 −9	−39 −50 −39	−34 −26 +7	-	Histology on seven patients only at two years; no change or deterioration
O'Brien *et al* (1990)[18]	16	8–12	Not specified	6	−42	−47	−56	−32	-	Appreciable improvement *v* placebo and baseline in histological score and grade
Poupon *et al* (1990)[21]	138	13–15	I (32)‡ II (47) III (39) IV (20)	6	−53	−47	−61	−41	−29	-

*Half received placebo and half received ursodeoxycholic acid. †Trial continued for nine months, although percentage fall in biochemical parameters given at three months. ‡Leuschner's and Poupon's studies are the only full papers and only in these is there sufficient data on patient characteristics; in both, placebo and treatment groups contained comparable proportions of histological grades. In Poupon's study, sex, age, and time since diagnosis were similar in both groups. Serum biochemical parameters were not significantly different at entry between placebo and treatment groups in either study, apart from higher alkaline phosphatase ($p<0.002$) in the treatment group in Poupon's study.
§Significant differences in all parameters in ursodeoxycholic acid group *v* placebo in all studies; however, in Hadziyannis's study no significant changes were noted in patients with late stage primary biliary cirrhosis or in those with serum bilirubin >171 μmol/l; fall in bilirubin not significantly different from placebo in O'Brien's study.

for biliary atresia.[31-34] These patients suffer from recurrent cholangitis, and it has been found that ursodeoxycholic acid may in some cases improve bile flow,[33] reduce episodes of cholangitis,[34] and result in improved weight gain.[31 34] Anecdotal reports suggest a benefit of ursodeoxycholic acid in cholestasis of pregnancy[35] and benign recurrent intrahepatic cholestasis.[36]

CHRONIC HEPATITIS

Ursodeoxycholic acid has also been observed to reduce transaminase levels in patients with chronic hepatitis.[3 14] Two double blind controlled trials have been reported: one, comprising 59 blood donors with raised alanine transaminase, found a significant reduction in alanine transaminase with ursodeoxycholic acid, with reversion to baseline levels when treatment was stopped.[37] The other study found no benefit of serum enzymes or liver histology in patients with non-A non-B chronic hepatitis (85% had antibodies to hepatitis C virus) followed up for one year.[38] This was a small trial (20 patients), however, and large spontaneous fluctuations in alanine transaminase are characteristic of such patients.

Mechanisms of action of ursodeoxycholic acid

It is clear from the results of clinical studies that ursodeoxycholic acid results in improvement of enzyme markers reflecting hepatocellular necrosis as well as cholestasis. It is more hydrophilic than the endogenous bile acids chenodeoxycholic acid and deoxycholic acid, though whether it is more hydrophilic than cholic acid is debatable.[2] It is less surface active than the more hydrophobic bile acids[2] and thus has less tendency to partition into membranes and to solubilise membrane lipids.[39 40] Consequently, it is less toxic to a variety of cells studied in vitro, including mast cells,[39] red blood cells,[41] and isolated hepatocytes.[42 43] The most hydrophobic bile acids, as expected, are the most toxic. Furthermore, ursodeoxycholic acid protects against the cytotoxic effects of other hydrophobic bile acids both in vitro and in vivo[41-43] by stabilising the cell membrane into which bile acids seem to be incorporated.[15]

The effects of bile acids in intact animals have been elegantly shown in a series of experiments from Kitani's group,[44-46] who found that infusions of hydrophobic salts in increasing concentrations produced an initial choleresis followed by profound cholestasis indicated by a fall in bile flow and bile acid secretion rate. Coadministration of ursodeoxycholic acid, however, inhibited cholestasis even when a hydrophobic bile acid was infused at high rates. The same group observed that ursodeoxycholic acid prevented biliary leakage of lactate dehydrogenase and albumin induced by hydrophobic bile acids in the rat, indicating that damage to bile duct epithelium was being prevented.[46] This protective effect is still seen if the concentration of ursodeoxycholic acid is a quarter that of the hydrophobic bile salt, suggesting it is not simply due to dilution of the more toxic bile sale.[1] Prevention of cholestasis may simply be a result of the more general membrane protecting effect of ursodeoxycholic acid (discussed above) exerted on the bile canalicular membrane. Indeed, it protects artificial membranes only if they are rich in cholesterol,[47] as is the case for the bile canalicular membrane.

Erlinger and Dumont have shown that unconjugated ursodeoxycholic acid is capable of producing a bicarbonate rich hypercholeresis,[48] which could be the result of either cholehepatic recycling of protonated ursodeoxycholic acid[4] or direct stimulation of hepatocyte bicarbonate transport.[1 48] Unconjugated ursodeoxycholic acid might be excreted by the hepatocyte when supraphysiological doses have been given so that the glycine/taurine conjugation mechanisms are saturated. The fact that no increase in unconjugated ursodeoxycholic acid is found in duodenal bile of patients treated with this compound[49] does not contradict this hypothesis, since cholehepatic recycling does not require the unconjugated bile acid to appear in the final bile.[48]

What relevance does this have to human liver disease? In primary biliary cirrhosis serum concentrations of hydrophobic bile acids, including toxic atypical bile acids, are increased.[50-53] Administration of ursodeoxycholic acid results in enrichment of the bile acid pool at the expense of endogenous hydrophobic bile acids. The mechanism probably involves competitive inhibition of active terminal ileal transport of conjugates of endogenous bile acids by ursodeoxycholic acid conjugates, thus enhancing faecal excretion of the former.[4] It seems likely that this is an important component of the mechanism of action of ursodeoxycholic acid in human liver disease, since cirrhotic patients with primary biliary cirrhosis, who, as observed previously, respond poorly to ursodeoxycholic acid treatment, do not show the expected decrease in endogenous bile acids.[53] The additional protective effects seen in animal and in vitro experiments contribute to the efficacy of ursodeoxycholic acid. In this respect there is emerging evidence that treatment results in more rapid hepatic transit and biliary excretion of endogenous bile acids in primary biliary cirrhosis, as assessed by hepatic handling of the taurocholate analogue selenium homocholic acid taurine (^{75}SeHCAT).[54] The proposed mechanisms of action of ursodeoxycholic acid are summarised in the Figure.

With regard to the hypercholeresis induced by ursodeoxycholic acid, it has been suggested that this could prevent sludging of bile in fine biliary radicles.[4] This mechanism might be particularly important in patients with cholestatic liver disease associated with cystic fibrosis in whom bile ducts are plugged by viscid mucus. Interestingly, it seems that much higher doses are necessary for an effect in this condition than in other cholestatic diseases.[27 55] Some other effects of ursodeoxycholic acid may be relevant clinically. Thus it is known that hepatobiliary transport of organic anions such as bilirubin is enhanced by most bile acids,[1] which may explain why many clinical trials have found a reduction in serum bilirubin in patients with primary biliary cirrhosis when on ursodeoxycholic acid treatment (Table). Too heavy a load of

ursodeoxycholic acid in severely jaundiced patients may have the opposite effect, possibly by non-competitive inhibition of hepatic uptake.[1] This may in part explain the reduced efficacy of the compound in late stage primary biliary cirrhosis.

Finally, some intriguing work has suggested that ursodeoxycholic acid might have another completely different mechanism of action. It is known that in cholestasis there is an increased expression of HLA class I antigens on hepatocytes and class II antigens on biliary epithelium. Class II antigens are targets for cytotoxic T cell damage.[56] Class I antigen expression probably also plays a part in cell mediated cytotoxicity. Calmus and his coworkers have found that aberrant class I expression on hepatocytes is reduced by ursodeoxycholic acid treatment, and they speculate that this might lead to a reduction in piecemeal necrosis.[57] Thus there may be an additional benefit from ursodeoxycholic acid in reducing immunological injury in primary biliary cirrhosis.

Conclusions and speculations

CURRENT CLINICAL ROLE OF URSODEOXYCHOLIC ACID IN LIVER DISEASE

Ursodeoxycholic acid should now be regarded as having a central role in the medical management of cholestatic liver diseases, in particular primary biliary cirrhosis, primary sclerosing cholangitis, neonatal biliary atresia, and liver disease associated with cystic fibrosis. The reasons for this are the strong evidence that ursodeoxycholic acid improves cholestasis and reduces hepatocellular damage in these conditions; the lack of adverse effects of the compound; and the absence of alternative treatments combining efficacy with lack of adverse effects. The longterm effects on liver histology and prognosis are not yet known, but the available evidence suggests that histology may improve with ursodeoxycholic acid. Caution should be exercised in patients in late stage primary biliary cirrhosis (stages III and IV). The dosage of ursodeoxycholic acid should be around 10 mg/kg/day for primary biliary cirrhosis and sclerosing cholangitis,[58] though higher doses may be appropriate in cystic fibrosis.[27 55] In chronic active hepatitis available evidence does not presently support a clinical role for ursodeoxycholic acid, though it remains to be determined whether a subsidiary role exists in conjunction with established treatments.

FUTURE RESEARCH

The results of large multicentre trials of ursodeoxycholic acid currently in progress will be needed before it is known whether liver histology is improved in patients with primary biliary cirrhosis. Longer term controlled studies will then be necessary to determine if the short term effect is maintained and whether there is an effect on prognosis. These could be mounted once the current trials are completed (assuming a beneficial effect in the medium term is confirmed). It seems reasonable to surmise that a beneficial effect on prognosis would be to prolong the asymptomatic phase of the disease rather than arrest it, slowing progress towards cirrhosis and liver failure. Indeed, recent work shows that, contrary to previously held beliefs, asymptomatic primary biliary cirrhosis is associated with a reduction in life expectancy.[59] Because of this, and being mindful of the long experience of the use of ursodeoxycholic acid in gall stone disease suggesting a lack of adverse effects, early treatment might be advocated to achieve the maximum impact. This would also be the period in which any effect on reduction of immunological injury would be most productive. Therefore it should not be unethical to mount longer term studies in asymptomatic patients. Given the different mechanisms which are thought to produce liver injury in primary biliary cirrhosis, it may also be appropriate to consider combining a drug specifically targeted at the immune system with ursodeoxycholic acid in future trials.

Other cholestatic liver diseases, in particular those associated with primary sclerosing cholangitis and cystic fibrosis, are at present virtually untreatable, so large multicentre controlled trials are urgently needed. Since these diseases share a common feature with primary biliary cirrhosis, namely accumulation of toxic hydrophobic bile acids, it is not unreasonable to hope that ursodeoxycholic acid treatment will be beneficial. It will be interesting to discover whether hypercholeresis has any relevance to clinical efficacy, particularly in cystic fibrosis. It would be useful to know whether ursodeoxycholic acid is of value in chronic hepatitis when given in combination with interferon alfa.

The emergence of ursodeoxycholic acid as a promising new treatment in a variety of chronic liver diseases is not only a hopeful development for clinical practice but also provides a stimulus to further research into the underlying mechanisms of liver damage in cholestasis. The next few years should provide some exciting new insights, together with detailed clarification of the clinical role, applications, and mechanisms of action of the compound.

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