Clinical Pharmacokinetics of Therapeutic Bile Acids

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Summary

The pharmacokinetics of chenodeoxycholic and ursodeoxycholic acids are reviewed in this article. Chenodeoxycholic acid is well absorbed by the intestine, whereas the absorption of ursodeoxycholic acid is incomplete. They are extracted efficiently by the liver, conjugated with glycerine and taurine, secreted in bile, and then undergo enterohepatic circulation with the endogenous bile acids. Therapeutic bile acids are metabolised by intestinal bacteria to lithocholic acid which is mainly excreted with faeces.

Since the large majority of bile acid is confined within the enterohepatic circulation (resulting in low serum concentrations) their volume of distribution is relatively high. Despite the high hepatic extraction, the clearance of therapeutic bile acids is relatively low because of the highly efficient enterohepatic recircu-
lation. Elimination of therapeutic bile acids mainly occurs in the faeces either unmodified or after biotransformation.

At present the main clinical indication for therapeutic bile acids is ursodeoxycholic acid treatment for chronic cholestatic liver disease. In these patients, ursodeoxycholic acid is efficiently absorbed but its hepatic uptake and biliary secretion are impaired, thus leading to reduced biliary enrichment and high serum concentrations of this exogenous bile acid. In patients with cystic fibrosis-associated liver disease, bile acid malabsorption also occurs, thus indicating the need for higher dosages.

The volume of distribution and clearance of ursodeoxycholic acid reduced in the presence of liver disease. Also in this case, elimination mainly occurs with the faeces but, in the presence of severe cholestasis, renal clearance may become relevant. Sulphation or conjugation with glucose and N-acetylg glucosamine facilitate urinary excretion.

Bile acids have been in widespread clinical use for more than 2 decades, initially for gallstone dissolution\cite{1,2} and more recently for the treatment of chronic cholestatic liver diseases.\cite{3} Chenodeoxycholic acid (CDCA) was the first bile acid to be approved for the treatment of patients with cholesterol gallstones; however, the frequent occurrence of diarrhoea and hypertransaminasaemia limited its use. Ursodeoxycholic acid (UDCA), the 7β-epimer of CDCA (fig. 1), was found to be at least as effective as CDCA at dissolving cholesterol gallstones, with virtually no adverse effects and consequently became the drug of choice for this indication. The litholytic mechanism of both of these bile acids involves reducing cholesterol oversaturation of the bile. At present, CDCA is still used clinically for gallstone dissolution, although now it is used in combination with UDCA;\cite{4} CDCA is also of value in the treatment of patients with inborn errors in bile acid synthesis.\cite{5,6}

The finding of a relationship between hydrophobicity of bile acids and their hepatotoxic properties, as well as the serendipitous observation of improvements in serum transaminases in several patients with gallstones and concomitant chronic hepatitis who were administered UDCA,\cite{7} suggested a possible role for this hydrophilic bile acid in the therapy of chronic liver disease. Subsequently, many clinical trials of UDCA in a variety of chronic cholestatic liver diseases established biochemical and clinical improvements, and also suggested a delay in progression of primary biliary cirrhosis (PBC), with the result that UDCA has now become an accepted treatment modality for chronic cholestatic liver disease.\cite{3,8}

Initially, it was considered that the choleretic properties of UDCA, coupled with its ability to cause a marked shift in the hydrophobic/hydrophilic balance of the bile acid pool, accounted for its mechanism of action.\cite{9} In recent years it has become apparent that UDCA is capable of exerting direct effects at the cellular, subcellular, and molecular levels. For example, it has been shown that UDCA interacts with cell membranes,\cite{10} affects cellular signal transduction,\cite{11-13} protects against mitochondrial damage,\cite{14} and exerts a variety of immunomodulatory effects.\cite{15}

The aim of this review is to describe the pharmacokinetics and metabolism of therapeutic bile acids in patients with gallstones and normal liver function and in patients with liver diseases. Excellent reviews of the pharmacokinetics of both CDCA and UDCA have been published, relating to their use in gallstone patients with normal liver function.\cite{16-18} More recently, several reviews have focused on the clinical aspects of UDCA therapy in chronic liver diseases.\cite{3,19,20} In contrast, little information is available on the pharmacokinetics of UDCA in patients with chronic liver diseases. This is perhaps due to: