SUMMARY

Sulfated glycolithocholic acid, a major metabolite of the secondary bile acid lithocholic acid in newborns, is highly cholestatic when administered to experimental animals. Its taurine conjugated analogue, on the other hand, is less hepatotoxic. This thesis deals with the pathophysiology of the potentially toxic lithocholic acid sulfates and the possibilities of dietary intervention to prevent their toxic effects.

It was found that elevated serum levels of sulfated lithocholic acid conjugates in children develop during the course of cholestatic liver disease, due to the well documented shift of bile acids from the enterohepatic to the systemic circulation and/or their increased formation in the liver during cholestasis. However, elevated serum levels may also be the result of an increased influx of these compounds from the intestine, as appeared from reproducible postprandial elevations in serum concentration of the sulfated bile acids after a standardized test meal in a specific group of patients, which could be prevented by addition of cholestyramine to the test meal (Appendix paper 1).

Animal studies aimed at the characterization of the enterohepatic circulation of sulfated lithocholic acid conjugates have been performed in unanesthetized and unrestrained rats with normal feeding behaviour, in which the enterohepatic circulation could be interrupted and restored without direct surgical intervention (Appendix paper 2). The use of pento barbital-anesthesia significantly affected the process of bile formation as well as intestinal bile acid absorption in the rat (Appendix paper 3).

Sulfated lithocholic acid conjugates were efficiently absorbed from the intestine when administered at physiological infusion rates. Absorption was not appreciably inhibited by excess of unsulfated bile acids. However, the presence of excess of calcium in the intestinal lumen selectively reduced their absorption (Appendix paper 4). Sulfated lithocholic acid conjugates were secreted into bile without further hepatic metabolism; urinary secretion was negligible under non-cholestatic conditions. The mechanism of their biliary secretion, studied in rats with an undefined genetic defect in biliary secretion of organic anions, was shown to be different from that of unsulfated bile acids, and probably identical to that of organic anions as bilirubin and dibromosulphthalein (Appendix paper 5).

Low doses of enterally administered sulfated glycolithocholic acid caused a reduction of the biliary secretion of phospholipids and cholesterol, without affecting bile acid secretion and bile flow. This may have been due to interference of the sulfated compound with intracellular lipid transport to the bile canaliculi, or to effects at canalicular level, e.g. by disturbing micellar aggregation. This reduction of biliary lipid secretion may be an initiating event in sulfated glycolithocholic acid-induced cholestasis (Appendix paper 6).

Cholestasis was readily induced by intravenous administration of relatively small amounts of sulfated glycolithocholic acid in rats with a depleted endogenous bile acid pool. The presence of endogenous bile acids prevented this cholestatic action, by 1) acceleration of the biliary elimination of the toxic compound, and 2) the maintenance of a high bile flow, which prevented precipitation of the compound in bile canaliculi and/or ductuli (Appendix paper 7). The differences in the hepatotoxic properties between sulfated glyco- and taurolithocholic acids may, at least partly, originate from their differential interactions with calcium; the former rapidly precipitated with calcium in a 1:1 stoichiometry in vitro, whereas the latter did not. Formation of calcium- sulfated glycolithocholic acid complexes may be an important factor in the development of cholestasis in vivo (Appendix paper 8).

Protection of the liver from sulfated lithocholic acid-induced hepatotoxicity can theoretically be exerted at hepatic level by: 1) increasing the availability of taurine for conjugation by dietary means. However, pharmacological doses of taurine are required to alter the pattern of bile acid conjugation significantly in man. 2) maintenance of a high bile flow to accelerate the biliary excretion of the
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toxic compounds and to prevent their precipitation in the hepatobiliary system. Protection in vivo is probably mainly mediated at intestinal level, by withdrawal of the cholestatic sulfated bile acids from the enterohepatic circulation. Binding of sulfated lithocholic acid conjugates to insoluble calcium phosphate in the intestinal lumen (Appendix paper 8) may be of physiological importance in this respect.

INTRODUCTION

The formation of bile is a complex process of the liver. Bile is a yellow-green, clear fluid, containing or consisting of a solution, containing or dissolved in water, a number of organic constituents, including electrolytes and trace elements (3). The main organic constituents of bile are phospholipids, cholesterol, bile acids, and bilirubin, the latter two being produced by the extrinsic and intrinsic pathways, respectively. In addition, bile contains a number of endogenous substances and certain xenobiotics, in many cases requiring conversion in the liver. The bile acids are essential for the elimination of bilirubin and a number of endogenous compounds and certain xenobiotics, in many cases requiring conversion in the liver. The bile acids are essential for the elimination of bilirubin and a number of endogenous compounds and certain xenobiotics, in many cases requiring conversion in the liver.

The bile acids are major detergents, in that they maintain water solubility of hydrophobic compounds such as cholesterol and bilirubin in solution (3). A significant aspect of bile acid function is the stabilization of the production of micelles containing fatty acids and monoglycerides and the transport of water-soluble vitamins in the aqueous phase of the micelles. The bile acids are also essential for the absorption of lipophilic substances such as cholesterol and bilirubin, conserved in an efficient way. The bile acids are also of major importance in the maintenance of normal bile flow and hepatic bile acid concentrations at the site of bile acid action.

Cholestasis refers to a condition in which bile flow is decreased or absent, or where bile is altered during cholestasis, including the presence of certain xenobiotics, in many cases requiring conversion in the liver. The bile acids are essential for the elimination of bilirubin and a number of endogenous compounds and certain xenobiotics, in many cases requiring conversion in the liver. The bile acids are essential for the elimination of bilirubin and a number of endogenous compounds and certain xenobiotics, in many cases requiring conversion in the liver.