Bile acid metabolism in hepatobiliary diseases

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ENTEROHEPATIC CIRCULATION OF BILE ACIDS

Bile acids are formed in the liver from cholesterol, and before their excretion into bile they are conjugated at their carboxyl groups with the amino acids glycine or taurine. Monohydroxy bile acids in addition are in part sulphated at their hydroxyl group.

After their excretion in bile and intestine the bile acids are deconjugated and dehydroxylated by the intestinal flora. Most of the bile acids are re-absorbed by diffusion in the jejunum or by active transport in the ileum and return via the portal blood to the liver. Only 10% of the bile acid pool is excreted by the faeces per day.

URINARY AND BILIARY EXCRETION OF BILE ACIDS

In patients with hepatobiliary diseases the biliary excretion of bile acids may be diminished (Figure 5.1), increased concentrations of bile acids appear in the peripheral blood and are excreted by the urine. In patients with biliary obstruction urinary excretion becomes the main route of bile acid excretion.

In patients with hepatobiliary diseases many bile acids can be detected in urine which are not present in healthy man. These bile acids include 3β-hydroxy-5-cholenoic acid, hyodeoxycholic acid, hyocholic acid, tetrahydroxy bile acids and many others. The appearance of these atypical bile acids (Figure 5.2) is the result of abnormal hydroxylation reactions in the liver.

Another alteration of bile acid metabolism in hepatobiliary diseases represents the sulphation and glucuronidation of bile acids at their hydroxyl groups. While in healthy man only monohydroxy bile acids are sulphated in greater amounts, patients with hepatobiliary diseases also
Figure 5.1 Enterohepatic circulation of bile acids in patients with hepatobiliary diseases. Plasma concentrations of bile acids increase and lead to increased urinary excretion of bile acids sulphate and glucuronide di- and trihydroxy bile acids. More than 70% of the bile acids excreted in urine are sulphated or glucuronidated. Sulphation of bile acids decreases with the number of hydroxyl groups. The position of the hydroxyl group is of importance for the glucuronidation, with 6α-hydroxyl groups being a preferred substrate. Tetrahydroxy bile acids are excreted in urine only in the non-sulphated, non-glucuronidated form. The majority of bile acid sulphates and bile acid glucuronides is in addition conjugated with taurine or glycine.

In the bile of patients with hepatobiliary diseases the proportion of sulphates and glucuronides is much smaller than in urine. Studies on the quantitative excretion of these molecules in bile of patients with cirrhosis of the liver indicate, however, that the biliary excretion of bile acid sulphates is 10 times greater and the biliary excretion of bile acid glucuronides is 20 times greater than in urine. It can be expected, however, that in the more severe forms of cholestasis the urinary excretion of sulphated and glucuronidated bile acids will become more important.

TURNOVER OF BILE ACIDS IN HEPATOBILIARY DISEASE

Data on the kinetics of bile acids are available for the non-sulphated, non-glucuronidated and for the sulphated bile acids but not for the glucuronides. In patients with cirrhosis of the liver, pool sizes and synthesis rates of cholic