109 DIRECT MEASUREMENT OF HEPATIC EXTRACTION OF CHENODEOXYCHOLIC AND URSEDOXYCHOLIC ACIDS IN MAN

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Since no estimates of ursodeoxycholic acid (UDCA) extraction and only indirect estimates of the hepatic extraction of chenodeoxycholic acid (CDCA) have been reported in normal subjects, and since patients with gallstones receiving CDCA or UDCA may have liver disease, we have measured the direct hepatic extraction of (1) 14C-CDCA in 8 control patients and 10 with liver disease (2) 14C-UDCA in 4 controls and 10 with liver disease. Ten controls were studied during cardiac catheterisation using a continuous infusion technique. Two controls and the patients with liver disease received an intravenous bolus of 14C-CDCA or 14C-UDCA during transvenous liver biopsy.

The extraction ratio of 14C-CDCA was 63 ± 3% (mean ± SEM) and of 14C-UDCA 63 ± 1%, in controls. In patients with mild liver disease, extraction was slightly impaired (14C-CDCA: 49 ± 15%, p<0.05; 14C-UDCA: 43 ± 5%, p>0.05), while with more severe liver disease (low serum albumin), it was greatly reduced (14C-CDCA: 16 ± 8%, p<0.001; 14C-UDCA: 7 ± 1%, p<0.001).

The results suggest (1) direct measurements confirm the accuracy of indirect measurements (van Berge Henegouwen & Hofmann, 1977, Gastroenterology, 73, 300-309) of hepatic CDCA extraction (2) hepatic extraction of CDCA is lower than of cholic and glycocholic acids (Gilmore & Thompson, 1980, Gut, 21, 123-127), but higher than of UDCA. (3) progressive impairment of CDCA and UDCA extraction occurs as the severity of liver disease increases.

110 LIVER DAMAGE IN CHOLESTEROL-FED RABBITS, ATTRIBUTED TO LITHOCOLATE PRODUCTION AND AMELIORATED BY 3,5,5',-TRIMETHYLCYCLOHEXANOL (TMC)

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Lithocholic acid is a minor constituent of normal rabbit gallbladder bile. In animals fed a 2% cholesterol diet for 9 weeks, biliary lithogenic index increased. Analysis by g.l.c.-m.s. showed that lithocholic acid accounted for 15.4% (+ 3.53 S.E.M.) of total bile acids whereas chenodeoxycholic acid, its usual precursor, was virtually absent. Only 0.6% of total bile acids were sulphated. Histological examination of liver tissue showed changes consistent with lithocholate toxicity, including hepatocyte ballooning, reticulin framework collapse and frank fibrosis. Changes were assessed as severe in 3, moderate in 4, and mild in one out of 8 animals. One rabbit developed jaundice. Concurrent treatment with TMC, a major metabolite of cyclandelate ("Cyclospasmol" (R), Brocades) was associated with reduced biliary lithocholate levels (p<0.05) and less hepatic damage (changes moderate in 4, mild in one, 3 entirely unaffected). "Rowacho" (R) (Rowa) was ineffective.

CONCLUSION: Increased biliary lithocholic acid may arise by direct conversion of dietary cholesterol in the rabbit, whose inability to sulphate bile acids promotes persistence in the enterohepatic circulation of lithocholate so produced. These changes may explain the occurrence of jaundice in the cholesterol-fed rabbit, in which TMC treatment may be mildly "hepatoprotective".

111 MECHANISMS FOR ADJUVANT CHOLELITHOLYTIC PROPERTIES OF THE MONOTERPENE MIXTURE RONACHOL (R)

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R (Rowa Ltd., Co.Cork, Eire) is an inexpensive, non-toxic proprietary choleretic. Each 0.1 ml capsule contains the following 6 monoterpenes - menthol (32%), menthone (6%), pinene (17%), borneol (5%), cineole (2%), camphene (5%). In acute (48 hr.) studies in man, R, like Chenodeoxycholic acid (CDCA), desaturates bile (Gut 20, 312 1979). Chronic administration of R (3 capsules daily for 6-9 months) to a group of cholesterol gallstone patients who underwent cholecystectomy had the 4 following effects:- 1) a 60% reduction (P=0.016) in hepatic HMGCoA reductase activity (the rate-limiting enzyme for cholesterogenesis), 2) gallbladder bile was only slightly less lithogenic than controls despite 3) a highly significant (P<0.001) elevation in the total biliary lipid content (9.3 ± 2.5 vs 5.3 ± 3.2 g/100 ml) 4) gallbladder volume assessed cholecystographically increased (P<0.05). Effect 1) confirms previous animal studies (Biochem. Pharmac. 29 2128 1980). Effect 2) could explain R's comparatively weak cholelitholytic properties when given alone and effect 3) (J.C.I. 61, 998 1978) why R plus low dose CDCA (375 mg daily) is so much more effective than either drug given separately (B.M.J. 282, 611 1981). The percentage of our patients withdrawn from cholelitholytic therapy because of biliary symptoms seems comparatively low. This and effect 4) may reflect menthol's spasmylic properties (B.M.J. 4, 835 1979).

We are currently assessing R plus CDCA in slightly larger dosage (7.5-10 mg/kg/day). The combination is well tolerated and a gallstone dissolution rate (partial or complete) after only six months treatment of 45% (n = 22) in an unselected group of patients is most encouraging.