77 PHENOBARBITAL (P) INCREASES CHOLESTASIS IN LIVER DISEASE - A HAZARD TO INFANTS?

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Urinary bile acid excretion was studied by gas chromatography/mass spectrometry in 4 infants with intrahepatic cholestasis and pruritus, aged 4-20 months, before and after administration of P (10 mg/kg/day). Serum levels of bilirubin and bile acids decreased but the activites of γ-glutamyltransferase (S-GT) and alkaline phosphatases (S-ALP) mainly increased.
Most infants increased their total bile acid excretion in urine by 4-fold. The percentage polyhydroxylated bile acids increased much more: before treatment tetra-OH-bile acids ranging from 0 to 7.6% (mean 2.4%) and after 3 to 100 weeks of treatment from 4.8 to 25.5 % (mean 17.2%) of total urinary bile acids ($p<0.001$). The predominant bile acids after treatment were cholic acid, 1,3,7,12 and 3,6,7,12 tetra-OH-5 β-cholanoic acids and hyocholic acid. Excretion of chenodeoxycholic acid was mainly unchanged. The relative amounts of sulphated bile acids decreased in all cases after treatment, before being 52-68% (mean 60%) and after 13-56% (mean 33%).
Although serum bilirubin levels decreased and polyhydroxylated bile acid excretion increased after P treatment, the increase of S-GT and S-ALP and the increased urinary excretion of cholic acid and total bile acids suggest more severe cholestasis. Our results indicate that further studies are necessary to show if P is beneficial in cholestatic disease in infancy. It might, on the contrary be a hazard in early infancy, and at present a routine administration to cholestatic infants is not recommended.

78 S-ADENOSYLMETHIONINE (SAMe) REVERSES TOTAL PARENTERAL NUTRITION(TPN)-ASSOCIATED CHOLESTASIS.

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The quantity of perfused amino acids (aa), and their qualitative pattern, was thought to be a pathogenic factor of TPN-associated hepatotoxicity. Previous studies have shown an hypothetic protective effect of methyl donor aa. To assess whether and how SAMe could normalize bile flow during infusion of aa with dextrose, 4 groups of rats (157-180g) were studied after 5 days of TPN (Vamin(V) or Travasol(T) with and without SAMe), as well as a weight matched control group (C) receiving dextrose IV and chow orally. Concentration of methyl donor aa was higher in V than in T. On TPN, the animals received 10.2 g of glucose and 3.4 g of aa daily. After TPN, bile flow was measured and hepatocyte membranes were prepared and their composition determined. Results of bile flow and hepatocyte membrane Na+K+ATPase activity are tabulated above :

	V+SAMe	V	T	T+SAMe
Bile flow (µl/min)	10.9±0.3	11.1±0.7*	8.5±0.9*	11.4±1.0
Na+K+ATPase (@)	14.6±3.6	14.7±1.7**	6.3±0.6**	17.1±2.9

@ = µM Pi/mg prot/h; *= p <.025; **= p <.001; n=6 in each group. Results in C group were similar to V, V+SAMe and T+SAMe. The membrane lipid and protein constituents showed few modifications. Conclusions : the significant decrease of Na+K+ATPase activity indicates an impairment of the bile acid independent flow and membrane fluidity by Travasol which could be restored by the simultaneous administration of SAMe.

79 ALTERED BILE ACID METABOLISM IN BENIGN RECURRENT INTRAHEPATIC CHOLESTASIS.

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The mechanism(s) involved in the initiation and perpetuation of an episode of cholestasis is unknown in patients with benign recurrent intrahepatic cholestasis (BRIC). There is evidence from animal experiments that sulphated monohydroxy bile acids can cause cholestasis, especially during a state of reduced bile acid poolsize.
Bile acid metabolism was studied in 10 BRIC patients in a cholestasis free period. Primary bile acid poolsizes were estimated simultaneously using deuterated cholic acid (CA) and chenodeoxycholic acid (CDCA). The poolsize of CA and CDCA expressed in µmol/kg bodyweight were significantly contracted in BRIC patients: 8.0±4.2 and 11.7±4.7, respectively, versus 24.1±11.7 and 22.9±7.8 in controls. Fractional turnover rates (day^{-1}) for CA and CDCA were increased 0.70±0.29 and 0.58±0.27, respectively, versus 0.29±0.12 and 0.23±0.10 in controls. Bile acid pool composition in % in BRIC patients was CA 34±17, CDCA 38±9, deoxycholic acid (DCA) 27±18, lithocholic acid (LCA) 1±1 with a glycine/taurine conjugation G/T ratio of 6.7±4.9. The percentage of sulphated bile acids never exceded 2% of the total amount of bile acids. Corresponding values for 32 controls were: CA 57±13, CDCA 29±9, DCA 14±9, LCA <1 and a G/T ratio of 2.4±1.3. Faecal bile acid loss in µmol/kg/day was 11.2±9.0 in BRIC patients compared to 2.8±1.4 in controls. The serum 7αOH-cholesterol and 26OH-cholesterol in nmol/L were increased significantly in BRIC patients 326±179 and 247±54, respectively, versus 171±90 and 198±64 in controls. These results suggest that in BRIC patients increased spill-over of bile acids to the colon occurs which leeds to increased faecal bile acid loss and a reduced bile acid pool size. Elevated serum 7αOH-cholesterol and 26OH-cholesterol are probably indicative for an accelerated bile acid synthesis rate, due to increased activity of 7α-hydroxylase and 26-hydroxylase, the enzymes catalyzing the first step in the two known pathways of bile acid synthesis. It is suggestive that cholestatic agents in a contracted pool might initiate an episode of cholestasis.

80 HEPATITIS B VIRUS (HBV) CARRIER STATE AND HLA ANTIGENS IN 13 ITALIAN FAMILIES.

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The rate of HBV persistence in the families of our patients affected by Chronic Hepatitis B is much higher (72%) than the chronicity rate reported in the Italian population (10%). AIMS: in order to investigate the possible influence of the major histocompatibility complex upon the course of Hepatitis B infection through a regulation of the host's immune response, we studied the phenotype frequencies of HLA class I and class II antigens in some families. PATIENTS and METHODS: 13 families were studied (56 subjects: 26 parents and 30 children). They all have been infected by HBV: 40 have been positive for HBsAg for longer than 1 year, 16 seroconverted to HBsAb positivity. HLA antigens typing was performed using the standard NIH lymphocyte microlymphocytotoxicity technique. (NIH standard for A and B, NIH long for DR and DQ). RESULTS: DR4, whose protective role against virus persistence has been reported in the literature, is totally absent in our study-group, whereas its frequency in a population of 526 healthy Italian controls (matched for geographical origin) is 18.5%. We used Fisher's exact test to compare the frequencies of HLA determinants in the 40 chronic HBV carriers with those of the 16 seroconverted subjects. A possible protective role was found for DR2 ($p= 0.0023$), while a possible linkage with HBV persistence was found for A3 ($p= 0.011$) and B35 ($p= 0.020$). CONCLUSION: the absence of DR4 and DR2 and the presence of A3 and B35 could play a role in HBV persistence. Further studies are going on to confirm these data in a larger population.

81 DEFICIENT INTERLEUKIN(IL)-2 PRODUCTION IN CHILDREN WITH CHRONIC B HEPATITIS (CBH).

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It is known that children with CBH have low levels of T lymphocytes espressing IL-2 receptors and that in adults affected by CBH there is a reduced production of IL-2. The aim of this study was to evaluate the production of IL-2 by lymphocytes following stimulation with phytoaemoagglutinin (PHA) in a group of children with CBH. Nine children (6 males) affected by CBH were investigated.The mean age was 9y-6m, and the mean duration of the disease was 3y-2m. The aspartate-amino transferase (AST) levels varied between 2 and 8 times the normal values (NV), with the majority having 3 times above the upper normal limit. All subjects were HBsAg positive ("+"). 6 children were HBeAg "+", 3 of whom were also anti-HDV "+", and 3 were HBeAb "+", of whom 2 had anti-HDV antibodies. The serum levels of IgG were increased in 8 patients. The liver biopsy, performed in 5 children, showed histological features of chronic active hepatitis in 3 and cirrhosis in 2. 8 age and sex matched healthy children were studied as controls. IL-2 production was obtained by peripheral blood mononuclear cells stimulated with PHA (1mcg/ml) after monocytes were removed by plastic adhesion. The activity of IL-2-containing supernatants was tested using PHA-induced blast cells by H3-thymidine incorporation. Levels of IL-2 are expressed as units/ml according to Saxena et al.(1) The mean value (34.78 U/ml) was significantly lower in CBH children when compared to controls (105.37 U/ml;$p<0.05$). This preliminary study indicates that IL-2 production is impaired in CBH children. This could explain the immunological alternations seen in CBH patients.

1) Saxena S. et al. Clin. Exp. Immunol. 63: 541, 1986.

82 A CONTROLLED TRIAL OF RECOMBINANT IFN-α TREATMENT DURING 3 MONTHS OF CHRONIC HEPATITIS B IN CHILDREN.

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Chronic hepatitis B virus (HBV) infection in children may lead to hepatic cirrhosis and hepatoma. The antiviral effect of recombinant interferon (rIFN) in the treatment of chronic hepatitis in adults has been proven. For this reason, we carried out a controlled study of therapy using rIFN-α in children with chronic hepatitis due to HBV.

A total of 24 children (2-12 years) were randomly allocated in two groups: control (n=12) and treatment (n=12), who received 10 MU of rIFN-α2A (Roferon)/m^2 body surface, I.M., thrice weekly during 3 months. All of them had a histological diagnosis of CAH and were HBsAg, HBeAg and HBV-DNA positive for at least 6 months before entry into the study.

The treatment was well tolerated and all children completed the study. At the end of the treatment period, 3 out of the 12 (33%) treated patients, became HBV-DNA negative. Another treated patient lost HBV-DNA at the 6th month and a total of 4 patients remained like that until the 12th month of follow-up. None of the controls lost HBV-DNA during the first six months of the study but 2 patients belonging to this group became HBV-DNA negative at the 9th month and another 2 at the 12th month. A total of 4 treated patients and 3 controls were HBeAg negative at the 12th month of follow-up. A marked decrease in ALT levels, among the four responder children was observed. In contrast no variations among non-responders were detected.

In summary, rIFN-α therapy in CAH-HBV infection in children is well tolerated. In addition, an antiviral effect was observed. Our previous results suggest that prolonged therapy (6 months, thrice weekly) could be useful in the treatment of children with chronic HBV infection