T85

INVESTIGATION INTO THE EFFECTS OF FK352 (A NOVEL ADENOSINE-1 RECEPTOR ANTAGONIST) IN CIRRHOTIC PATIENTS WITH ASCITES: A PILOT STUDY.

AJ Stanley, EH Forrest, KJ Dabos, PC Hayes.
Dept. Medicine, Royal Infirmary of Edinburgh EH3 9YW.

Cirrhotic patients have a characteristic hyperdynamic systemic circulation and evidence of renal vasoconstriction and tubular dysfunction, maximal in patients with ascites. These renal abnormalities are reproduced by stimulation of adenosine (ADO)-1 receptors in the kidney.

Aim: To assess the systemic and renal effects of a novel ADO-1 antagonist (FK352) in cirrhotic patients with ascites.

Patients: Eight cirrhotic patients (4 males) were studied (mean age 52.3 years (3.3), mean CPS 8.1 (0.5)). None were taking vasoactive medications and diuretics were stopped 1 week prior to the study.

Methods: Urine and plasma were collected at half hourly intervals for 2 hours before and 2 hours after administration of 10mg (first 4 patients) or 25mg FK352 (next 4 patients) to measure absolute sodium excretion (Ur. Na), free water clearance (H20 Cl.) and estimate GFR and renal plasma flow (RPF) using inulin and PAH clearance methods. Unilateral renal vein flow (RBF) (thermodilution method), cardiac index (CI) and systemic vascular resistance index (SVRI) were measured prior to and following drug administration.

Results: Pre and post drug administration results are summarised:

	Ur. Na (umol)	Ur. volume (ml)	H2O Cl (ml/min)	RBF (ml/min)
Pre-	209.7(106.5)	207.8(53.3)	3.8(1.2)	451.7 (146.5)
Post-	549.0(159.5)	392.5(84.3)	7.9(2.2)	589.0 (154.3)
p value	p<0.01	p=0.02	p=0.05	p<0.05

No changes were seen in CI or SVRI. Clearance results are awaited.

Conclusion: ADO appears to have a role in the renal impairment seen in cirrhosis, acting via ADO-1 receptors. ADO-1 specific antagonism offers a new therapeutic approach to the management of cirrhotic ascites and the associated renal dysfunction.

T87

TAURINE SUPPLEMENTATION OF PARENTERAL NUTRITION SOLUTIONS DOES NOT INCREASE THE PROPORTION OF BILE ACIDS CONJUGATED TO TAURINE IN PREMATURE INFANTS

Horslen SP, Watson S, Manning N, Tanner MS.

Cholestasis associated with parenteral feeding has a multifactorial aetiology. Premature infants are at particular risk. Taurine is thought to be poorly synthesised in preterm infants. Taurine deficiency has been shown to cause decreased bile flow in experimental animals and it has been hypothesised that a relative taurine deficiency may contribute to the cholestasis seen in newborn infants receiving parenteral nutrition (PN).

Infants were recruited to the study once a clinical decision was made to commence PN. Each infant was randomly assigned to receive either standard (taurine-free) amino acid solution or a taurine-enriched solution. Plasma samples taken on day 7 of PN were analysed for bile acid species and state of conjugation by liquid-solid extraction and gas chromatography-mass spectrometry.

77 (38 receiving taurine) infants were enrolled into the study of which 30 (17 receiving taurine) remained on PN at 7 days. No significant difference was found in the number of infants in each group developing cholestasis (10 of 38 receiving taurine and 5 of 39 on taurine-free solutions). There was also no difference in the proportion of plasma bile acids conjugated to taurine between the two groups. In both groups taurine conjugated bile acids predominated over glycine conjugates with a geometric mean ratio of taurine: glycine conjugates of 1.92:1 in the taurine supplemented group and of 2.06:1 in the unsupplemented group.

In conclusion this study does not support the hypothesis that taurine supplementation of preterm infants receiving PN develop less cholestasis and furthermore the data appear to show that the preterm infant is able to synthesise taurine.

Paediatric nutrition T86–T87

T86

EFFICACY AND SAFETY OF SUPPLEMENTARY NASOGASTRIC FEEDING IN CHILDREN UNDERGOING BONE MARROW TRANSPLANTATION

A Papadopoulou, A McDonald*, MD Williams*, PJ Darbyshire*, IW Booth
Institute of Child Health, University of Birmingham and *The Children's Hospital, Birmingham

Nutritional insult following bone marrow transplantation is complex and its nutritional management challenging. Enteral nutrition (EN) is cheaper and easier to provide than parenteral nutrition, but its tolerance and effectiveness in reversing nutritional depletion following BMT is poorly defined. We therefore prospectively assessed nutritional status, well being and nutritional biochemistry in 21 children (mean age 7.5 years; 14 males) who received nasogastric feeding following BMT (mean duration of 17 days) and in 8 children (mean age 8 years, 4 males) who refused enteral nutrition and who received dietetic advice only. **Results :** Enteral nutrition was stopped prematurely in 6 patients. Greater increases in weight (p=0.0005), and mid arm circumference (p=0.01), were observed in the EN group, while positive correlations were found between the duration of feeds and improvement in weight (r=0.75; p<0.0001), and in mid arm circumference (r=0.74; p=0.0004). Vomiting, diarrhoea and fever were not more frequent in the EN group, while febrile episodes and diarrhoea tended to have a quicker duration than in the dietetic counselling group (p=0.05 and p=0.06, respectively). Diarrhoea occuring during EN was not associated with fat malabsorption, while carbohydrate malabsorption was associated only with rotavirus infection. However, enteral feeding did not affect bone marrow recovery, hospital stay, the general well-being of patients, or serum albumin concentrations. Hypomagnesaemia, hypophosphataemia, zinc and selenium deficiency were common in both groups. In conclusion, enteral nutrition when tolerated is effective in reversing nutritional insult following BMT. With existing regimens nutritional biochemistry should be closely monitored in order to provide supplements when required.

Basic science T88–T101

T88

GASTRIN PRECURSORS ARE PRESENT IN ADENOMAS IN THE MOUSE POLYPOSIS COLI MODEL - APC1638N.

A. M. Smith[1], S. A. Watson[1], J. Coaker[2], P. Clarke[1], J. C. Mathers[2], R. Fodde[3], A. Varro[4], J. D. Hardcastle[1].
[1] Dept. of Surgery, University of Nottingham,[2] Dept. of Biological and Nutritional Sciences, University of Newcastle,[3] University of Leiden, [4] Dept. of Physiology, University of Liverpool.

The hormone gastrin is now a well recognised growth factor for colorectal adenocarcinomas. The gastrin gene has been shown to be activated in colorectal tumour cells, and precursor gastrin species have been identified. The precursor glycine-extended gastrin-17(gly G-17) has been shown to have a proliferative effect, and it has been postulated that it acts via an autocrine growth loop.

The mouse model of polyposis coli, APC1638N, which contains a stable mutant APC gene leads to the spontaneous production of intestinal and extraintestinal tumours, similar to the phenotype seen in human familial adenomatous polyposis. The aim of this study was to evaluate the role of gastrin precursors in the adenoma-carcinoma sequence.

METHODS.In this study mice were fed a high fat Western style diet. At termination the mice were examined and samples were taken from normal colonic mucosa and neoplasms which ranged from adenomas with moderate dysplasia to carcinoma-in-situ. Specimens were formalin-fixed, paraffin sections made and stained with polyclonal antisera directed against progastrin, gly-G17 and amidated G17. Binding of the primary was detected using the avidin-biotin complex technique. The samples were assessed for site and degree of staining.

RESULTS. Progastrin was present in all the neoplastic samples and 7/8 normal mucosa. The intensity of staining of progastrin was greater in the neoplastic samples than in normal samples. In addition, in normal mucosa progastrin was confined to the cytoplasm of epithelial cells compared to widespread cytoplasmic staining together with stromal and luminal edge staining, indicative of secretion. Gly-G17 was present in 9/10 neoplastic samples in the cytoplasm and stroma but was absent in normal mucosa. No mature amidated gastrin was found in any sample.

CONCLUSIONS. There was evidence of over expression and secretion of progastrin and de novo expression and secretion of gly-G17 in neoplastic tissue from adenoma to carcinoma-in situ. This indicates that progastrin/gly-G17 mediated autocrine pathways may be early events in the adenoma-carcinoma sequence. Furthermore this model may be useful in assessing the efficacy of novel anti-gastrin therapies such as the immunogen, Gastrimmune in pre-malignant conditions.

This study was funded by Aphton Corporation, California, USA.