INTRODUCTION

Patients undergoing surgery for oro-pharyngeal malignancies are often malnourished. This may impair their post-operative recovery and their tolerance of subsequent adjuvant therapy. Naso-gastric (NG) tube feeding is often instituted post-operatively but is associated with particular problems in such patients. Many of these may be overcome by use of per-cutaneous endoscopic gastrostomy (PEG) feeding. AIMS To compare the efficacy of pre- and post-operative feeding via a PEG tube with the standard management of pre-operative dietary advice and post-operative NG feeding. METHODS Patients referred for oro-pharyngeal tumour resection who had a body-mass index less than 25 were randomised to receive either PEG feeding with Jevity, 2-4 weeks before surgery, continuing for at least four weeks post-operatively, or standard dietary advice pre-operatively and naso-gastric feeding afterwards. Changes in nitrogen balance, anthropometric indices, pre-albumin levels and other biochemical parameters were assessed.

RESULTS Twenty-four patients entered the study; 12 in each group. Four patients from the Jevity/PEG group withdrew prior to surgery, 3 because their tumour was unsuitable for resection at operation and 1 because of complications unrelated to PEG insertion. One patient in the control group was unsuitable for surgery and 5 withdrew after the 10-day post-operative visit, 3 because they required a PEG tube on clinical grounds and 2 were lost to follow-up. The mean change in nitrogen balance between post-operative days 1 and 10 was 14.13g for the Jevity/PEG group and 6.53g for the controls (p=0.037). The Jevity/PEG group gained a mean of 0.07kg from pre-surgery to day 10 whereas the control group lost a mean of 2.9kg over the same period (p=0.049). Improvements in pre-albumin levels were also seen in the Jevity/PEG group but these did not reach statistical significance. CONCLUSION PEG feeding initiated prior to oro-pharyngeal cancer surgery is more effective at maintaining body weight and nutritional status than standard management.


Aim: To compare gains in body weight and lean body mass with changes in quality of life in an undernourished outpatient population. Methods: 131 poorly rehabilitated patients with chronic disease (19 short bowel, 18 oesopagia, 13 inflammatory bowel disease, 12 pseudoobstruction, 9 neurological dysphagia, 3 chronic pancreatitis, 33 poor intake, 24 others), presenting sequentially to a nutrition support clinic, were divided into those with a body mass index (BMI) of less than the desirable range of 20-25 (group 1) and those with an index within the desirable range at presentation (group 2). The parameters was for weight, and lean body mass in group 1 and maintenance in group 2. Anthropometric measures and Nottingham Health Profile (NHP) quality of life (QOL) scores were recorded at presentation. These were repeated subsequently and a review was performed in July 1995.

Interventions: Dietary advice, oral supplements, nasogastric feeding, percutaneous endoscopic gastrostomy feeding, home parenteral nutrition. Results: Followup data were available for 105 patients. Weight gain occurred in 84.8% of group 1 (with a mean gain of 4.24kg (p=3x10^-5)). Lean body mass increased by a mean 2.06kg in group 1 (p=0.0008). There was no statistically significant weight change in group 2. For group 1 there was a statistically significant improvement in every category of QOL score (Energy p<0.001, Pain p<0.01, Emotion p<0.01, Sleep p<0.01, Social isolation p<0.05, Mobility p<0.05), but no statistically significant improvement occurred in any category for group 2. Conclusion: Restoration of body weight and lean body mass is associated with significant improvement in quality of life indices in chronic illness.

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Introduction: Gastro-oesophageal reflux (GOR) of acid is known to be associated with oesophageal pathology as well as symptomology. The role that duodenal reflux plays, however, is less well known. Bilitec 2000™ spectrophoto- metric bilirubin detector, has for the first time allowed ambulatory monitoring of duodenogastro-oesophageal reflux, so symptoms can be related to the presence of duodenal contents as well as acid in the oesophagus.

Methods: 28 consecutive patients referred for further investigation of symptomatic GOR underwent oesophageal manometry and combined oesophageal pH and Bilitec monitoring. All symptom events described as regurgitation or heartburn were analysed for the presence of pH < 4 and Bilitec absorptions. Two minutes either side of the symptom. Acid (pH < 4) shift and bilirubin absorbance were analysed for the total, supine and upright periods.

Results: 15 patients (53%) had significant acid reflux on pH testing, and 13 patients (47%) did not. Sixteen patients (57%) had significant bile reflux on Bilitec monitoring and 12 patients (43%) did not. There was good correlation between total bile and acid reflux (p < 0.05, Spearman rank correlation). 168 symptom events were identified in 28 patients (range 0-24 events per patient).

Of the 69 symptom events that were not associated with either an acid or a bile reflux episode, 51 (74%) occurred in patients with no significant acid or bile reflux. The majority of events occurred in the upright interprandial period (78 events, 46%), 53 events (32%) occurred during the postprandial period, 31 events (18%) in the supine period and 6 events (4%) during meals.

Conclusions: 12 patients (4%) had no significant acid reflux and 12 patients (43%) had no significant bile reflux, but there are presumably other pathologies to explain the 51 symptoms in these patients (3 had abnormal motility patterns). However, it appears that symptoms were more frequent associated with acid reflux than bile reflux, and that duodenal contents are not the major cause of symptoms when there is a good correlation between acid and bile reflux.

IDENTIFICATION OF CORTICAL LOCI PROCESSING HUMAN OESOPHAGAL SENSATION USING POSTERION EMISSON TOMOGRAPHY


Aims: To identify the cortical loci which process nociceptive and non-nociceptive human oesophageal sensation. Methods: 8 healthy subjects were studied, 7 male, age range 24-47 years. Oesophageal stimulation: was performed by repeatedly infusing a 2 cm balloon placed in the oesophagus 35 cm from the nose at a frequency of 0.5 Hz. Balloon volume inflations were adjusted to produce either no sensation (BASE), nociceptive sensation (SENS) or non-nociceptive sensation (PAIN).

Positron Emission Tomography (PET): Each subject underwent two PET scans for each sensation level. 800-1000 MBq of H215O was injected for each scan. Magnetic Resonance (MR) scans: were performed in each subject to aid in anatomical localisation. Analytic: PET data were corrected for movements, coregistered with MR scans and stereoformalised. ANCOVA corrected r-images depicting the contrasts SENS vs BASE, PAIN vs BASE and PAIN vs SENS were created. Statistical significance of the implicated areas was assessed using the spatial extent of clusters with r > 2.5. Results: Non-nociceptive stimulation: (SENS vs BASE) elicited bilateral activations along the basal parts of the central sulcus and the caudal parts of the anterior insular cortex (p < 0.05). Nociceptive stimulation: produced activations of the same areas, albeit stronger (z-score PAIN vs BASE: 4.95 and SENS vs BASE: 4.06). In addition more basal parts of the right anterior insular cortex and the anterior cingulate gyrus were also activated (p < 0.05 for both SENS vs BASE and PAIN vs SENS). Discussion: Flow decreases during SENS or PAIN states compared to baseline were detected. Notable among these was the right prefrontal cortex (Brodmann area 10/12), which showed up in a highly consistent manner in both the PAIN vs BASE and the SENS vs BASE contrasts. Conclusion: Although cortical areas which process non-nociceptive and nociceptive oesophageal sensation overlap, nociceptive sensation is exclusively processed in the right anterior insular cortex and the anterior cingulate gyrus.

DOES CISAPRIDE IMPROVE OESOPHAGEAL FUNCTION AND PREVENT SYMPTOMATIC RELAPSE AFTER HEALING OF OESOPHAGITIS? N. McQuaid, RGP Watson, H. Collins, RJ McFarland, AHG Love. Dept of Medicine, Queen’s University Belfast, Northern Ireland, UK.

Introduction: Reflux oesophagitis can be healed by proton pump inhibitors in up to 90% of cases. However most patients relapse within 1 year of stopping treatment. Cisapride has been shown to improve lower oesophageal sphincter pressure (LASSP) but its role in preventing relapse after healing is unclear.

Aims: To determine if maintenance therapy with cisapride after healing of oesophagitis improves parameters of oesophageal function and reduces the rate of symptomatic relapse when compared with placebo.

Methods: Patients with frequent heartburn and grade II-III oesophagitis were treated with omeprazole (OME) 20mg BD for 4-14 weeks. Those with endoscopically confirmed healing at the end of treatment were randomised in a double blind fashion to receive maintenance therapy with either cisapride (CIS) 20mg nocte or placebo (PL) for up to 6 months, and antacids p.r.n. (all patients). Oesophageal pH monitoring, manometry and symptomatic assessment were performed before starting and after 4 weeks maintenance therapy.

Results: Forty two patients (26 male, mean age 51 years, range 26-78yrs) were randomised - 21 to each treatment group. There were no significant differences between the two groups in age, gender, severity of symptoms or grade of oesophagitis at initial diagnosis. On completing OME therapy, only 3 patients in each group had reflux symptoms daily or weekly. After 4 weeks on maintenance therapy, 19 (90%) of the CIS group and 16 (76%) of the PL group had developed daily or weekly heartburn (p = 0.4). Seventeen (76%) of the CIS group and 12 (57%) of the PL group withdrew from maintenance therapy due to symptomatic relapse (p = 0.2). LASSP significantly improved (from 16.4 to 21.9mmHg) in the CIS group (p = 0.01) but not in the PL group (25.5 to 20.8mmHg, p = 0.2). The LASSP improvement in the CIS group was significantly greater than that in the PL group (p = 0.007). All other parameters (mean distal peristaltic amplitude, duration and velocity, median 5% pH time < 4, duration and number of reflux events) showed no significant difference between the two groups and no significant improvement.

Conclusion: Maintenance therapy with cisapride 20mg nocte improved the LOPS in patients whose oesophagitis had been healed with OME. However the rate of symptomatic relapse on CIS was not significantly better than with placebo, and 76% of those on CIS maintenance required reintroduction of OME within 4 weeks.

IDENTIFICATION OF CORTICAL LOCI PROCESSING HUMAN OESOPHAGAL SENSATION USING POSTERION EMISSON TOMOGRAPHY

N. Trudgill, M. D’Amato, S. Rile, Northern General Hospital, Herries Road, Sheffield, S5 7AU and Rotta Research, Monza, Italy.

A fat meal decreases lower oesophageal sphincter (LOS) pressure and increases transient LOS relaxations (TLOSR). These effects may be mediated by cholecystokinin (CCK).

We have studied the effects of CCK antagonism with loxiglumide on LOS function following a fat meal. Nine healthy volunteers (6M, 20-29 years) were studied on two separate occasions more than 72 hours apart. Each subject was infused with a manometric assembly incorporating a Dent sleeve and a pH probe. Following a 60 minute basal period, subjects were given an intravenous infusion of loxiglumide or placebo in random order. A 200 kcal long chain triglyceride meal (Caloglen) was then infused into the stomach and manometric and pH data was recorded for a further two hours.

Basal LOS pressure during placebo fell from median 17.2(range 10.5-23.5)mmHg to 7.2(1.1-18.8) after 15 minutes, 8.6(7.6-22.4) after one hour and 12.9(7.1-24.8) after two hours. Loxiglumide significantly attenuated this fall, basal LOS pressure falling from 15.2(8.8-20.3) to 13.7(8.2-21.1) after 15 minutes (p = 0.01 cf. placebo), 12.2(4.9-20.1) after one hour (p = 0.05) and 12.9(5.5-17.2) after two hours (p = ns). There was a reduction in both the number of TLOSR and reflux episodes during loxiglumide infusion, but these differences did not reach statistical significance ( TLOSR placebo 10(0-12), loxiglumide 2(0-6); reflux episodes placebo 0(0-14), loxiglumide 0(0-8)).

Loxiglumide attenuates the fall in basal LOS pressure following a fat meal in healthy volunteers. Endogenous CCK is therefore implicated in the control of LOS function and studies in patients with reflux disease are indicated.
Clinical significance of overexpression of c-erb-B2 and relationship to proliferation and p53 accumulation in oesophageal cancer.

Mr Y Mohsen FRCS, Dr R Conrad FRCP and Mr M Winall MS FRCS, Department of Surgery, Royal Free Hospital and school of medicine, Pond street, Hampstead, London NW3 2QG.

The incidence of oesophageal carcinoma is increasing at a rate higher than any other cancer worldwide. Patients with this disease typically have poor prognosis. Reports suggest that c-erb-B2 expression may be of value in the prognosis of breast, ovarian and gastric cancer. The c-erb-B2 proto-oncogene encodes a growth factor receptor which is over-expressed in a variety of carcinomas. 100 archival oesophageal cancer specimens were analysed immunohistochemically using monoclonal antibody to the product of the oncogene to detect over-expression of c-erb-B2. 18% of the tumours were membrane positive for c-erb-B2, the staining being located at the cell membranes, 51% showed distinctive cytoplasmic staining. The expression of c-erb-B2 was correlated with Cell Proliferation index, accumulation of p53 protein and clinicopathological parameters. Statistical analysis demonstrated a correlation between c-erb-B2 expression, cellular proliferation index (p<0.01) and level of p53 accumulation (p<0.01). No statistically significant correlation with age, survival, stage, lymph node or distal metastases, histological type and differentiation was found. An almost significant correlation was noted for histological differentiation (p<0.07). Established prognostic factor, stage, correlated well with survival. Our results suggest that the presence or absence of c-erb-B2 protein is not a prognostic indicator in cases of oesophageal carcinoma. c-erb-B2 expression may be related to cell proliferation and p53 accumulation but not to the extent of influencing prognosis. The significance of cytoplasmic expression of c-erb-B2 is unclear.

Gastric fundal tone, sensation and the relaxation response to a nitric oxide donor, in health and reflux oesophagitis. M Newton, MA Kamm, WR Bunham, LM Akkermans, St. Mark’s Hospital, Northwick Park, Harrow; Oldchurch Hospital, Romford, Utrecht University Hospital, The Netherlands.

Background: The fundus is thought to play a major role in the afferent control of lower oesophageal (LOS) function, and fundal adaptive adaptation after a meal has been shown to be impaired in patients with gastro-oesophageal reflux disease (GORD). Nitric oxide (NO) is an important relaxant of the fundus postulated that fundal tone, compliance and nitric oxide sensitivity may be important in patients with GORD.

Methods: 8 patients with erosive oesophagitis (Savary Millard grades I-III) (5 male; median age 55, 32-71y) and 10 healthy controls (5 male; median age 35; range 23-55y) swallowed the folded bag of a gastric barostat after a six hour fast. All were lying at 30° from horizontal. Minimal distending pressure (MDP) (pressure required to produce an intrabag volume >50ml) and gastric compliance (3ml/dpr) were determined by increasing intrabag pressure in 2mmHg increments. The pressures required to produce initial sensation and maximum tolerated sensation were recorded. With the intrabag pressure set at MDP+2mmHg sublingual glyceryl trinitrate (GTN) (500mcg) was administered and the percentage change in intrabag volume from initial volume recorded.

Results: The minimal distending pressure was significantly greater in patients than controls (3.3-5.2 vs 2.5-2.6mmHg; median, range; patients vs controls; p=0.016). Gastric compliance was similar in both groups (53 (33-75) vs 49 (27-75) ml/mmHg). In both patients and control symptom score increased with increasing intrabag pressure. There was no difference between groups in the pressure at first intragastric sensation (10.5 (4.19) vs 10 (8.16) mmHg above MDP) or in the maximal tolerated pressure (16 (8.23) vs 12.5 (12-16) mmHg above MDP). The maximum change in gastric volume response to GTN did not differ significantly between groups (40 (0-155) vs 9 (5-191) mmHg).

Conclusion: Minimal distending pressure, which is partly determined by resting fundal tone, appears to be elevated in patients with GORD, and may contribute to the reflux process. However fundal compliance does not appear to be altered in patients with GORD. There is major fundal relaxation in response to a nitric oxide donor, but the range of response in relation to a standard GTN dose is large. As a result there was no significant difference in the response to this exogenous nitric oxide donor.

Role of human papillomavirus (HPV) in Oesophageal cancer and its inter-relation with p53 and tumour proliferation.

Mr Y Mohsen FRCS, Miss L Barker FRCS and Mr M Winall MS FRCS, Department of Surgery, Royal Free Hospital and school of medicine, Pond street, Hampstead, London NW3 2QG.

Specific types of HPV have been closely linked with tumours of the ano-genital tract. Loss of p53 tumour-suppressor gene function can occur in a variety of ways, including gene mutation and interaction with the E6 protein of HPVs. Reports from high risk areas of oesophageal cancer have suggested that HPV infection is a risk factor. We studied 52 formalin-fixed, paraffin-embedded oesophageal carcinoma specimens for the presence of HPV and p53 expression, using a 3 layer with microwaving immunostaining technique. Tumour proliferation index was calculated based on immunostaining with the antibody MIB-1. 11 (21.2%) tumours demonstrated positive staining in the surrounding non cancerous epithelial cells of which only 4 (7.7%) demonstrated positive staining in the nuclei of cancer cells. 14 (26.9%) tumours were p53 negative (73.1%) demonstrated positive nuclear staining (Mean level 47.1 S.E. 4.7).Mean Tumour Proliferation index was 29.5% (S.E. 2.4). No correlation was found between presence of HPV protein in cancerous cell nuclei, levels of p53 expression or Tumour Proliferation index. Proliferation index showed a correlation with P53 expression (p<0.000). HPV does not appear to influence tumour proliferation rate nor levels of expression of mutant p53. The low prevalence of HPV protein in oesophageal tumours precludes any significant aetiological role. The finding contrast with previously reported HPV involvement in oesophageal lesions in high risk areas and concur with studies carried out in low risk areas. HPV cannot be viewed as a potential aetiological agent in the multifactorial pathogenesis of oesophageal carcinoma in low risk areas.
CLINICAL SIGNIFICANCE OF P53 EXPRESSION IN OESOPHAGEAL CANCER.

Mr. Yasir Mohamed FRCS, Dr Rod Conrad FRCP and Mr Marc Wisala MS FRCS
Department of Surgery, Royal Free Hospital and school of medicine, Pond street, Hamstead, London NW3 2QG.

The tumour suppressor gene p53 is believed to play an important role in the progression of human malignant tumours through mutation or over-expression. To examine the clinical significance of the expression and accumulation of P53 in oesophageal cancer, 100 formalin fixed paraffin-embedded, specimens of oesophageal cancer were analysed immuno-histochemically using a monoclonal antibody (DO-7, DAKO) and microwave oven heating method. Cell proliferation index for all tumours was calculated from immunostaining with the MIB-1 monoclonal antibody and correlated with clinical parameters as well as p53 status.

Of the 101 tumours 39% were adenocarcinoma, 54% squamous cell carcinoma, 3% oat cell carcinoma and 4% undifferentiated. 29% of all the tumours were P53 negative 71% p53 positive with a mean positivity percentage of 59.4 SD 25.4. The age, sex, site, tumour differentiation, lymph node status, distal metastases, treatment and survival was correlated to p53 status and cell proliferation index.

Correlation’s were found between p53 status / proliferation index (p<0.001), treatment, stage and survival (p<0.005). Overall the cumulative survival rate of patients with p53 expression was lower than that of the patients without expression (P<0.05). The prognostic value of p53 appears to be highly significant in surgically resected cases of squamous cell carcinoma (p<0.02).

Immunology T174–T183

OXIDATIVE STRESS IN ACUTE PANCREATITIS

Departments of *Surgery and *Chemical Pathology, Bristol Royal Infirmary, Bristol BS2 8HW.

Acinar cell injury in acute pancreatitis leads to an increased production of oxygen free radicals (OFRs). These may cause local and distant tissue damage by increasing capillary permeability. OFRs are scavenged by intracellular antioxidants and serum factors, principally albumin, urate, ascorbate, α-tocopherol, and retinol. A balance normally exists between the serum total antioxidant capacity (TAC) and OFRs. Potential for damage arises when the production of OFRs rises beyond the TAC.

TAC was measured by colourimetry in 23 patients with acute pancreatitis, on admission and daily for 5 days. Serum albumin and urate were also measured, as components of TAC. Malondialdehyde (MDA), a lipid fragmentation product caused by OFR peroxidation of phospholipid membranes, was measured as an indicator of oxidative stress. A control group consisted of 22 patients undergoing elective surgery. Results are expressed as medians [interquartile range]; statistical analysis was by Mann-Whitney U Test.

TAC was significantly lower in the pancreatitis group than the preoperative values for the control group, both on admission (1.4 [1.3-1.6] vs 1.6 [1.4-1.8]μmol/l, p=0.016) and on the day of the lowest measurement (1.3 [1.2-1.4]μmol/l, p=0.001, day 3). Both albumin (34 [31-37] vs 37 [34-41]g/l, p=0.017, on day 1; 31 [25-33] vs 37g/l, p=0.003, on day 3) and urate (243 [199-266] vs 381 [308-446]μmol/l, p=0.001, on day 1; 210 [192-281] vs 381μmol/l, p=0.001, on day 3) were also lower in the pancreatitis group than controls. MDA was higher in the pancreatitis group than in the control group (4.1[1.1-2.3] vs 1.2[0.8-1.9] on day 1) but this did not reach statistical significance.

These results indicate that serum TAC is reduced in acute pancreatitis. TAC may be insufficient to counterbalance increased OFR production, resulting in organ damage caused by oxidative stress. If low levels of TAC are found to correlate with organ damage, then its measurement may permit the identification of a patient group who might subsequently benefit from antioxidant therapy.

CBD-ASSOCIATED T CELLS ARE OLIGOCLINAL, SHOW CLONAL PERSISTENCE AND CYTOLYTIC ACTIVITY

*Brigham and Women’s Hospital and Beth Israel Hospital, Boston.

The phenotype of T lymphocytes associated with the common bile duct (CBD) is unknown. We investigated the hypothesis that they behave like other intraepithelial lymphocytes (IEL). We determined the phenotype, cytotoxic potential and T cell receptor (TCR) repertoire of T cells obtained during endoscopic retrograde cholangiopancreatography (ERCP). Three subjects were studies: two with primary sclerosing cholangitis (one as a complication of ulcerative colitis) and a third normal control. After establishing a short-term T cell line, cells were 1) stained with monoclonal antibodies for flow cytometric analysis, 2) used as effector cells for cytotoxicity and redirected lysis assays and 3) analyzed for TCR-β chain transcript expression. Flow cytometry revealed, that for all the subjects, 98% of the T cells were TCR-β positive with a CD4: CD8 ratio that ranged from 0.5 to 1.2. Redirected lysis studies showed that the normal CBD-derived T cell line had cytotoxic potential, that did not differ from that of a normal peripheral blood T (PBT) cell line; however, when the intestinal epithelial cell line, Caco-2, was used as a target the CBD-derived T cell line exhibited significantly more cytolytic activity in comparison to the control PBT line. CDR3-length displays suggested that all three CBD-derived lines were oligoclonal. This was confirmed by cloning and random sequencing of PCR amplification products after using TCR-β chain specific primer pairs; TCR-β chain sequences were reiterated in all Vβ-specific clones analyzed. In one case, two expanded TCR-β clones could be identified which were persistent in the bile duct over a period of one year. We conclude that the human common bile duct contains T cells which share several characteristics with intestinal IELs.