SHORT REPORTS

Loperamide and Ileostomy Output—Placebo-controlled Double-blind Crossover Study

Loperamide,* a newly synthesized antidiarrhoeal agent more potent than diphenoxylate (Lomotil)^{1,2} inhibits the peristalsis and the response to coaxial stimulation and nicotine in the isolated guinea-pig ileum, probably through a direct effect on nerve endings or intramural ganglia, or both.³ The present study was designed to analyse this inhibitory activity on human small intestinal peristalsis in vivo.

Materials and Methods

Twenty volunteers, aged 25-73, with well-established ileostomies for ulcerative colitis (13 patients), Crohn's disease (4), colonic polyposis (2), and colonic adenocarcinoma (1), were asked to weigh their daily ileostomy output with a precision tubular balance, continuing their usual daily activities and diet. After a three-day drug-free period, they were allocated at random to either seven-day loperamide/seven-day placebo sequence or the reverse. Each patient was given a bottle with 2-mg loperamide capsules and a bottle with identical looking placebo capsules for each treatment period and was asked to take two capsules twice a day for the first four days and, if needed, to adapt the daily dose to six capsules for the remaining three days of each period. Non-parametric tests⁴ were used for statistical evaluation.

Results and Discussion

The median and range of the daily faecal weights were 645 (100-2620), 500 (80-2010), and 660 (100-2020) respectively during the drug-free, loperamide, and placebo period. Individual data are summarized in the fig. There were no appreciable daily variations.

Effect of loperamide and placebo on daily ileostomy output

Daily faecal outputs were significantly lower during the loperamide period than during drug-free or placebo periods ($P < 0.001$). Median daily ileostomy output decreased by 22% in the loperamide period, and increased by 2% in the placebo period compared with the drug-free period. There was no correlation between the duration of the ileostomy and the faecal output. Sixteen of the 20 patients guessed the code correctly, whereas four were uncertain—though their faecal weights were obviously lower with loperamide. The total number of loperamide capsules taken during the last

*Loperamide (4-p-chlorophenyl)-4-hydroxy-N, N-dimethyl- α -diphenyl-1-piperidine butyramide hydrochloride (R18553), shortly available from Janssen Pharmaceuticals Ltd., Janssen House, Marlow, Bucks. SL7 1ET.

three days of the study period was much lower than the corresponding number of placebo capsules (median and range respectively 15, 5 (3-18), and 18 (9-18) ($P < 0.05$). During loperamide many patients noticed an increased urinary production and experienced an improvement in their ileostomy care and soiling accidents. There were few adverse experiences and these were probably not drug-related, except for one patient who complained of pain during the opening of his ileostomy because of increased stool consistency. Extensive laboratory tests showed no abnormal results.

We suggest that loperamide, by inhibiting small intestinal peristalsis, prolongs the intestinal transit time and thereby increases the water and salt absorption. Because of its effectiveness, its low incidence of side effects, and its lack of toxicity, loperamide is a reliable adjunct in controlling excessive ileostomy losses of water and electrolytes and so is advantageous in ileostomy care.

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Diagnosis of Miliary Tuberculosis by Transbronchial Lung Biopsy

In the last 20 years there has been a striking change in the clinical pattern of miliary tuberculosis, with a decrease in frequency but an increase in the number of undiagnosed cases and the age of affected patients.¹ Sputum smears and cultures are frequently negative, so that definitive diagnosis is delayed. We have recently seen a patient whose chest x-ray film showed a miliary pattern in whom miliary tuberculosis was diagnosed by transbronchial lung biopsy within 48 hours of admission. Effective chemotherapy produced a dramatic recovery.

Case History

A 71-year-old Negro was admitted to another hospital with a three weeks' history of lethargy. He had lost 30 lb (13.6 kg) weight over the preceding three months. His temperature was 38.7°C, pulse 108/min, respirations 24/min, and blood pressure 100/75 mm Hg. He was lethargic but oriented when aroused. Abnormal laboratory data included: leucocyte count $3.7 \times 10^9/l$, serum sodium 112 mmol/l. Chest x-ray films showed a diffuse interstitial infiltrate with a miliary pattern. Ziehl-Neelsen and auramine-rhodamine stains of the transtracheal aspirate were negative for acid-fast bacilli (A.F.B.). As the patient appeared septic, he was treated with broad-spectrum antibiotics pending culture results. He remained febrile and on the third day was transferred to Denver General Hospital with a temperature of 39.3°C. Miliary tuberculosis was now suspected with associated adrenal insufficiency or the syndrome of inappropriate secretion of antidiuretic hormone. Four hours after transfer he was given intravenous corticosteroids and started triple antituberculosis therapy. His fever abated and his confusion cleared within 12 hours. A fibreoptic bronchoscopy and a transbronchial biopsy were done on the third day. Tracheobronchial anatomy was normal; multiple bronchial brushings were obtained for stains, cultures, and cytologic evaluation. Four transbronchial lung biopsies were taken from the right lower lobe for culture and histological evaluation. A.F.B. stains of this tissue showed multiple organisms. Smears from the bronchial brushes stained for A.F.B. were negative, though cultures of the brushes were positive

for *Mycobacterium tuberculosis* at three weeks. The patient continued with corticosteroids and antituberculosis drugs, and at three months was discharged on a supervised outpatient programme.

Comment

Early bacteriological confirmation of miliary tuberculosis may be difficult to obtain. Compared with the relatively high incidence of a positive smear and culture in fibrocavitary tuberculosis, the sputum yield or organisms in miliary tuberculosis is relatively low.¹ Liver biopsy yields a fairly high percentage of granulomas but does not confirm the diagnosis unless the A.F.B. stain is positive. Bone marrow biopsies usually show granulomas when anaemia, leucopenia, and monocytosis are present; but the incidence of caseation and positive A.F.B. stains is low.² Many other diseases may cause miliary mottling in the chest x-ray films, and biopsy techniques have been developed to help in the differential diagnoses without the need for thoracotomy. Nevertheless, both percutaneous needle aspiration and cutting needle biopsy are associated with frequent pneumothoraces.³ Andersen described transbronchoscopic lung biopsy via the rigid bronchoscope. While only 16% of his cases had inconclusive biopsies, pneumothorax was frequent.⁴ In 24 of 33 patients who underwent transbronchial lung biopsy using a flexible fiberoptic bronchoscope a diagnosis was established without pneumothorax occurring.

We think that this is the first report of the diagnosis of miliary tuberculosis via transbronchial lung biopsy. As this patient had six negative sputum smears for A.F.B. before the procedure, the risk of infection to the bronchoscopist was thought to be minimal. This technique is safe and extremely efficacious in the rapid diagnosis of miliary lesions of the lung in acutely ill patients.

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Carcinoembryonic Antigen in Differential Diagnosis of Carcinoma of Pancreas from Chronic Pancreatitis

The differentiation of pancreatic carcinoma from chronic pancreatitis may prove impossible even at operation. Having heard that carcinoembryonic antigen (C.E.A.) levels were nearly always raised in pancreatic cancers^{1 2} we investigated both C.E.A. levels and Lundh test results as a means of differentiating these two conditions.

Methods, Patients, and Results

Plasma C.E.A. was measured by a modified double antibody technique.³ Pancreatic exocrine function was estimated by the Lundh test⁴ in all 25 patients with chronic pancreatitis and 10 of the 12 patients with carcinoma of the pancreas. Patients with chronic pancreatitis showed at least three of the following features: pancreatic calcification on abdominal x-ray films; a mean trypsin activity (M.T.A.) in duodenal juice after a Lundh test meal ≤ 6 IU/ml⁴; at least one well-documented attack of acute pancreatitis with serum amylase ≥ 1100 IU/l; diagnosis of chronic pancreatitis at laparotomy; history of chronic pancreatitis of three or more years. Pancreatic carcinoma was diagnosed at operation within two weeks of C.E.A. and duodenal M.T.A. determinations. In six patients histological confirmation was not obtained. The tumour was apparently confined to the pancreas in four, and either extended beyond the pancreas or had metastasized in eight.

Ten patients with pancreatitis but none with carcinoma had normal plasma C.E.A. levels (≤ 12.5 μ g/l; $\chi^2 = 6.95$; $P < 0.01$). No patients with pancreatitis had C.E.A. levels above 40 μ g/l compared with five of those with carcinoma ($\chi^2 = 12.27$; $P < 0.001$). The two diseases overlapped from 12.5 to 40 μ g/l and

only one of the four patients with localized carcinoma had a level greater than 40 μ g/l. C.E.A. values indicated malignancy in five patients (those with values greater than 40 μ g/l), but the Lundh test suggested a pancreatic carcinoma in seven patients (see table).

Diagnostic Value of Plasma C.E.A. and Lundh Test in 10 Patients with Carcinoma of Pancreas*

Case No.	C.E.A. (μ g/l)	M.T.A. (IU/ml)	Lundh Test (Bile in Duodenal Juice)	Test Indicative of Malignancy	
				C.E.A.	Lundh
1	24.0	2.9	—	—	+
2	54.0	1.1	—	+	+
3	43.9	2.2	—	+	+
4	38.5	4.9	—	—	+
5	25.5	3.1	—	—	+
6	230.0	0.5	—	+	+
7	27.0	2.9	—	—	+
8	48.5	Unsuccessful†	Unsuccessful†	+	—
9	500.0	33.9	+	+	—
10	15.0	8.4	+	—	—

*Patients in cases 1-8 were jaundiced.

†Tube failed to pass third part of duodenum.

Discussion

Though C.E.A. was once thought to be specific for adenocarcinoma of the gut abnormal values have been recorded in many benign conditions also.² Our results confirmed a high incidence of raised C.E.A. levels in patients with pancreatic carcinoma, but C.E.A.'s role in the differential diagnosis of pancreatic disease was disappointing. Up to a level of 40 μ g/l chronic pancreatitis and pancreatic carcinoma overlapped considerably, but we did not record levels greater than 40 μ g/l in chronic pancreatitis. In the five patients with carcinoma who had levels above 40 μ g/l the diagnosis was usually suspected on other evidence. Only one patient with a localized lesion had a C.E.A. level greater than 40 μ g/l.

The high incidence of positive C.E.A. assays (68%) in chronic pancreatitis was not unexpected because biological measurements are often abnormal in any disease. Others have reported high C.E.A. levels in up to 64% of patients with chronic pancreatitis, but the reason for this abnormality is not clear.⁵ We could not incriminate alcohol intake, smoking habits, length of history, pancreatic calcification, or other gastrointestinal diseases though others have suggested alcohol intake and associated liver disease as causes of raised C.E.A. levels. C.E.A. levels did not correlate with the extent of pancreatic exocrine insufficiency as measured by the Lundh test, but the test does not measure the amount of inflammation or developing fibrosis in the pancreas, and they may be important.

Most of our patients with pancreatic cancers were also jaundiced; in such cases a low M.T.A. and absence of bile in the duodenal juice strongly indicate malignancy. Therefore, it was not surprising that the additional information of the Lundh test increased the diagnostic accuracy from five to nine patients. Though in a larger series C.E.A. levels may indicate a malignant cause of pancreatic exocrine insufficiency the fetal pancreatic antigens may prove more specific. Thus, measuring C.E.A. alone is usually unhelpful in differentiating pancreatic carcinoma from chronic pancreatitis, but together with the Lundh test it may be helpful.

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