Gastrointestinal function in chronic radiation enteritis – effects of loperamide-N-oxide

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Abstract

The effects of loperamide-N-oxide, a new peripheral opiate agonist precursor, on gastrointestinal function were evaluated in 18 patients with diarrhoea caused by chronic radiation enteritis. Each patient was given, in double-blind randomised order, loperamide-N-oxide (3 mg orally twice daily) and placebo for 14 days, separated by a washout period of 14 days. Gastrointestinal symptoms; absorption of bile acid, vitamin B12, lactose, and fat; gastric emptying; small intestinal and whole gut transit; and intestinal permeability were measured during placebo and loperamide-N-oxide phases. Data were compared with those obtained in 18 normal subjects. In the patients, in addition to an increased frequency of bowel actions ($p<0.001$), there was reduced bile acid absorption, ($p<0.001$) a higher prevalence of lactose malabsorption ($p<0.05$) associated with a reduced dietary intake of dairy products ($p<0.02$), and faster small intestinal ($p<0.001$) and whole gut transit ($p<0.05$) when compared with the normal subjects. There was no significant difference in gastric emptying between the two groups. Treatment with loperamide-N-oxide was associated with a reduced frequency of bowel actions ($p<0.001$), slower small intestinal ($p<0.001$), and total gut transit ($p<0.01$), more rapid gastric emptying ($p<0.01$), improved absorption of bile acid ($p<0.01$), and increased permeability to ^{51}Cr EDTA ($p<0.01$). These observations indicate

that: (1) diarrhoea caused by chronic radiation enteritis is associated with more rapid intestinal transit and a high prevalence of bile acid and lactose malabsorption, and (2) loperamide-N-oxide slows small intestinal transit, increases bile acid absorption, and is effective in the treatment of diarrhoea associated with chronic radiation enteritis.

(Gut 1993; 34: 476-482)

Chronic radiation enteritis is now recognised as a frequent and clinically important sequel of abdominal and pelvic irradiation treatment for malignant disease.¹⁻⁵ Diarrhoea, with or without abdominal cramps, is the most common symptom.² Although intestinal stricture and associated bacterial overgrowth are well recognised in chronic radiation enteritis, in most cases the pathophysiology of the diarrhoea is uncertain. While changes in intestinal absorption and motility unrelated to bacterial overgrowth have been implicated in the aetiology of diarrhoea,^{1,2,4,6,7} there has been no comprehensive evaluation of gastrointestinal function in chronic radiation enteritis. Perhaps partly as a result of this, present approaches to treatment have often been empirical.^{1,5}

This study aimed to evaluate various aspects of gastrointestinal function in patients with diarrhoea caused by chronic radiation enteritis and the effects of treatment with the peripheral opiate agonist precursor loperamide-N-oxide.

TABLE 1 Characteristics of the patient group

Patient no	Age (y)	Body weight (kg)	Body mass index	Diagnosis	Radiation dose Gy/no of fractions/days	Radiation field (Size – cm × cm)
1	68	69.2	25.6	Carcinoma of cervix	44.95 Gy/25 F/32 (25 Gy to pt 'A' intracavitary)	16.5 × 18.5
2	80	71.9	24.8	Carcinoma of prostate	59.76 Gy/30 F/51	15.5 × 17.5
3	80	72.5	24.7	Carcinoma of prostate	62.15 Gy/31 F/44	15.5 × 19.0
4	63	58.8	27.7	Carcinoma of cervix	No details available (treated in Chile)	
5	76	62.5	27.6	Endometrial carcinoma	46 Gy/23 F/31	17.5 × 15.5
6*	79	66.0	23.5	Endometrial carcinoma	50 Gy/25 F/41 (20 Gy/vaginal mould)	17.5 × 18.0
7	85	58.0	23.6	Carcinoma of cervix	46 Gy/23 F/33 (20 Gy to Pt 'A' intracavitary)	16.0 × 16.5
8	90	54.0	21.3	Carcinoma of cervix	50 Gy/25 F/33 (20 Gy to Pt 'A' intracavitary)	15.0 × 16.0
9	70	54.0	22.5	Carcinoma of cervix	34 Gy/17 F/27 (45 Gy to Pt 'A' intracavitary)	14.0 × 15.0
10	42	62.0	22.2	Carcinoma of cervix	50 Gy/25 F/36	17.0 × 21.0
11	63	67.0	28.3	Endometrial carcinoma	50 Gy/25 F/32	15 × 28.5 (abdomen) 15 × 17.5 (pelvis only)
12	73	67.0	25.9	Carcinoma of cervix	50 Gy/25 F/39	14 × 19.5
13*	73	65.0	21.2	Carcinoma of prostate	64 Gy/32 F/47	13.0 × 19.5 (pelvis) 8.5 × 9.5 (prostate)
14	72	59.0	22.5	Carcinoma of cervix	50 Gy/30 F/45	15.0 × 14.0
15	78	70.0	29.2	Endometrial carcinoma	46.8 Gy/26 F/39 (20 Gy vaginal mould)	15.5 × 17.0
16	73	54.0	21.4	Carcinoma of ovary	50 Gy/26 F/39	15.0 × 18.0
17	81	74.0	25.3	Carcinoma of prostate	64 Gy/32 F/45	15.0 × 14.5
18	63	57.0	18.8	Carcinoma of ovary	49.9 Gy/25 F/35	15.0 × 20.0
19	48	114.0	51.4	Carcinoma fallopian tube	55 Gy/30 F/40	15.0 × 20.0
20	57	80.0	28.4	Endometrial carcinoma	50 Gy/25 F/35	Not available

*Patients withdrew from study.

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Accepted for publication
1 September 1992

Methods

SUBJECTS

Twenty patients (16 women, four men, median age 73 years (range 42–90), median body weight 65 kg (54–114 kg) and median body mass index (BMI) 25.1 (18.8–31.4)) with persistent diarrhoea 3–22 years after therapeutic pelvic irradiation for carcinoma of the genitourinary tract (see Table I for individual patient characteristics) were studied. Persistent diarrhoea was defined as a chronic doubling of the frequency of defecation before irradiation and a minimum frequency of at least 14 bowel actions a week. Patients who had had gastrointestinal surgery, apart from uncomplicated appendectomy, were excluded. Other criteria for exclusion were inflammatory bowel disease, pernicious anaemia, evidence of hepatic or renal dysfunction (any biochemical parameter for hepatic function exceeding twice the normal range or plasma creatinine >0.12 mmol/l, or both), and a constant requirement for medication (such as anticholinergics, anti-depressants, or non-steroidal anti-inflammatory drugs) which might influence gastrointestinal motility, or otherwise interfere with the evaluation of the test drug. Significant small intestinal strictures were excluded by small bowel radiological investigations.

Eighteen normal volunteers (11 women, seven men, median age 45 years (19–75), median body weight 75 kg (45–109 kg), and median BMI 26.0 (17.8–38.7) who had no history of gastrointestinal disease and were not taking any medication were also studied. The median age in the normal volunteers was less than that in the patient group ($p < 0.01$) but there was no significant difference in BMI between the two groups. All of the patients and all but one of the controls were white.

PROTOCOL

Each of the 20 patients was given, in double-blind randomised order, loperamide oxide tablets (Janssen Pharmaceutica Beerse, Belgium) in a dose of 3 mg twice daily by mouth (0800 h and 2000 h) and placebo (identical tablets without loperamide oxide) for 14 days, separated by a wash-out period of 14 days. Between days 3 and 14 after starting either loperamide oxide or placebo, each patient underwent measurements of the following aspects of gastrointestinal function: (i) gastrointestinal symptoms (day 14); (ii) absorption of bile acid and vitamin B12 (days 3 to 10), lactose (day 6), dietary fat and stool weight (day 10); (iii) gastrointestinal transit: gastric emptying, small intestinal and whole gut transit (day 7); and (iv) intestinal permeability (days 13, 14). Because of methodological practicalities, absorption of bile acid and vitamin B12 was determined before the measurements of gastrointestinal transit and intestinal permeability was measured last.

Each patient had a complete blood examination, multiple biochemical analysis of plasma, and ECG on recruitment into the study and at the end of each phase of the study. Any adverse effects from the trial medication were also documented at the end of each phase of the study.

The control subjects did not receive either placebo or loperamide oxide tablets but underwent an identical series of measurements on one occasion.

The study protocol was approved by the Ethics Committee of the Royal Adelaide Hospital on March 30, 1989 and each subject gave written informed consent.

MEASUREMENTS

Gastrointestinal symptoms

The following symptoms were assessed by questionnaire on entry into the study and at the end of each phase of the study⁸: (i) nausea, (ii) vomiting, (iii) abdominal pain, (iv) frequency of bowel actions (number of bowel actions per week) and stool consistency (hard formed, soft formed, loose or watery). Except for (iv), each symptom was scored according to the following classification: 0 – symptom absent; 1 – mild, symptom could be ignored if the subject did not think about it; 2 – moderate, symptom could not be ignored but did not influence daily activities; 3 – severe, symptom influenced daily activities.⁸ The total score (maximum 9) was then calculated for each phase of the study. The frequency and consistency of bowel actions for the 2 week periods on loperamide oxide and placebo and during the wash-out period were recorded in a diary. The number of bowel actions each week was calculated. The number of bowel actions in each three day faecal collection was also recorded.

A questionnaire was also used to record dietary intake of milk products and fat and the presence or absence of intolerance to milk or milk products (symptoms of nausea, abdominal bloating, abdominal cramps, or diarrhoea) after each subject had been enrolled into the study. Intake of dairy foods was expressed as calcium intake/week and fat intake was classified as 1 = low, 2 = medium, or 3 = high.⁹

Absorption

Bile acid and vitamin B12 absorption were determined by measuring the whole body retention at 7 days of selenium-75 labelled homotaurocholic acid (SeHCAT) and cobalt-58 labelled vitamin B12 (⁵⁸Co vitamin B12).¹⁶ On day 1, after a light breakfast of tea and toast at 0700 h, one capsule of ⁵⁸Co vitamin B12 (Amersham International) containing 30 kBQ ⁵⁸Co was swallowed with 30 ml water at 0900 h. The photo-peak counts corresponding to the 808 keV photon energy of ⁵⁸Co and the 265 keV photon energy of ⁷⁵Se (to correct for down scatter from the higher energy, ⁵⁸Co window into the lower energy ⁷⁵Se window) were recorded from a whole body counter. One capsule of SeHCAT (Amersham International) containing 37 kBQ ⁷⁵Se was then swallowed with 30 ml water. Four hours later the number of counts in both the ⁵⁸Co and ⁷⁵Se photo peak windows were determined.⁶⁷ This figure, after correction for room background counts (and down-scatter counts from the ⁵⁸Co into the ⁷⁵Se photo peak windows) was considered to represent 100% whole body

retention. There was no significant difference between the ^{58}Co counts at baseline and at 4 hours. Seven days later at 0900 h the counts in both ^{58}Co and ^{75}Se photo peak windows were again measured. This number, after correction for room background counts, radionuclide decay, and Compton scatter was used to derive the percentage whole body retention of bile acid and vitamin B12.^{6,7} Although the second measurement of vitamin B12 and bile acid absorption was made at least 4 weeks later, a correction for patient background counts was made by first counting the residual counts in both the ^{58}Co and ^{75}Se photo peak windows before the administration of the second doses of ^{58}Co vitamin B12 and SeHCAT. Otherwise an identical protocol was observed.

Dietary fat absorption was assessed by measuring the fat content in a 3 day collection of faeces, using a standard method modified for extraction of fatty acids into chloroform.¹⁰

Lactose absorption was assessed by measurement of breath hydrogen concentrations after an oral lactose load. Each subject fasted overnight and at 0900 h was given 50 g lactose dissolved in 200 ml water, after an antiseptic mouth wash and a baseline end expiratory breath sample had been taken. Subsequent end expiratory breath samples were obtained at least every 30 minutes for up to 4 hours. All breath samples were analysed for hydrogen concentration using a sensitive chromatographic method, capable of detecting concentrations as low as 1 ppm. A sustained peak in breath hydrogen greater than 10 ppm was taken to indicate malabsorption of lactose.¹¹ The day after the performance of this test, patients were asked (by one of the investigators who was unaware of the hydrogen analysis) whether symptoms of nausea, abdominal bloating, cramps, or diarrhoea occurred within 8 hours of the lactose load.¹¹

Gastrointestinal transit

At 0830 h, after an overnight fast (from 2200 h on

the evening before the test) each subject ingested 200 ml water containing 10 g lactulose (Duphalac-Duphar, Holland), 20 g dextrose, 40 mBq $^{99\text{m}}\text{Tc}$ -sulphur colloid and 50 radio-opaque plastic markers over a period of 2 minutes.^{12,13} The subject then laid supine under a wide field view gamma camera. A cobalt marker was placed at the right anterior superior iliac crest to aid alignment of images. Data were acquired for a minimum of 5 hours. For the first 30 minutes after meal completion data were sampled every minute, followed by 3 minute frames for the remainder of the study. End expiratory breath samples were taken at 10–15 minute intervals after ingestion of the meal for breath hydrogen analysis. During the study the subject was allowed to sit up, or walk around briefly if they wished every 60 minutes.

Regions of interest were drawn around the stomach and colon.^{12,14} After data were corrected for radionuclide decay, scatter, and gamma ray attenuation, using previously described methods,¹⁵ time-activity curves characterising gastric emptying and colonic filling were derived. By a process of computer subtraction a time activity curve representing small intestinal transit was also obtained.¹³

Time zero was considered the time of completion of the test meal. A sustained rise in the breath hydrogen concentration >5 ppm was considered to represent the arrival of the meal at the caecum.¹⁶ For gastric emptying, the lag phase before any of the meal emptied from the stomach and the 50% emptying time were determined.¹⁵ For small intestinal transit the following parameters were determined: (i) start of colonic filling (arrival of head of meal assessed scintigraphically and by breath hydrogen measurements)¹⁶; (ii) small intestinal transit (start of colonic filling minus the lag phase for gastric emptying); (iii) small intestinal residence (area under derived small intestinal transit time activity curve); (iv) time for 50% colonic filling.¹⁴ Whole gut transit was determined radiographically by the first arrival of the radio-opaque marker(s) and the time when 50% or more of the radio-opaque markers were in the stool.¹²

Intestinal permeability

This was assessed by two tests.

(1) *Urinary excretion of ^{51}Cr EDTA.* Each subject was initially asked to collect their urine for 24 hours. At 0930 h after an overnight fast (from 2400 h the subject ingested 2–10 ml of ^{51}Cr EDTA (Australian Atomic Energy Commission, code no CRIMI) containing 750 kBq of ^{51}Cr , followed by 300 ml water. Fasting was maintained for a further 2 hours, after which a normal diet was permitted. Patients were instructed to take no alcohol and to collect all urine for the next 24 hours. The entire 24 hour collection was counted in a large volume counter. The 24 hour urine collection before ^{51}Cr EDTA was also counted, to correct for any background radioactivity derived from ^{75}Se from the bile acid absorption test. The result was expressed as a percentage of administered dose.^{17,18}

(2) *Urinary excretion of a double sugar-lactulose/rhamnose.* After an overnight fast (from 2400 h,

TABLE II Results in patients during the placebo phase of the study and in control subjects

Parameter	Control	Patients (placebo)	p Value
No of subjects	18	18	
Calcium intake (mg/wk)	3155 (65–9486)	1475 (0–8190)	<0.02
Gastrointestinal symptoms:			
Score	0 (0–1)	0 (0–3)	NS
Bowel actions/wk	8 (3–14)	19 (9–53)	<0.001
Stool frequency/3d	4 (2–10)	7 (2–14)	<0.001
Stool wt/3d (g)	507 (308–1190)	450 (186–1275)	NS
Absorption:			
SeHCAT (%)	22.8 (9.2–63.6)	3.3 (0.0–45.7)	<0.001
^{58}Co Vit B12 (%)	81.4 (29.4–98.9)	74.3 (45.1–100)	NS
Faecal fat (mmol/3d)	53 (20–80)	33 (11–65)	<0.01
Lactose malabsorption (no)	2	10	<0.05
Gastrointestinal transit; gastric emptying:			
Lag phase (min)	0.5 (0.5–7.5)	0.5 (0.5–3.5)	NS
50% emptying (min)	65 (27–99)	55 (1–160)	NS
Small intestinal transit:			
Start colonic filling (min)	57 (23–117)	29 (14–73)	<0.001
50% colonic filling (min)	178 (88–295)	125 (83–208)	<0.001
Small intestinal transit (min)	52 (22–114)	28 (14–68)	<0.001
Small intestinal residence (AUC)	39.2 (23.2–57.7)	27.4 (18.6–46.8)	<0.01
Whole gut transit:			
First marker (h)	26.5 (6.5–48)	21.5 (6–45)	<0.05
50% markers (h)	32.5 (17.5–71)	28.5 (10–72)	NS
Intestinal permeability:			
^{51}Cr EDTA (%)	1.49 (0.70–4.06)	1.99 (0.091–8.25)	NS
Lactulose (mmol/l)	0.93 (0.14–16.3)	0.60 (0.04–9.8)	NS
Rhamnose (mmol/l)	1.85 (0.33–48.3)	1.91 (0.23–52.2)	NS
Lactulose/rhamnose (ratio)	0.095 (0.04–0.29)	0.060 (0.03–0.25)	NS

Data are median values and ranges (analysis by Mann-Whitney U test).

each subject was instructed to urinate at 0900 h and was then given 22.6 g glucose, 5 g lactulose, and 1 g L-rhamnose in 100 ml of distilled water. Thirty minutes after ingestion of the test solution the patient was encouraged to drink and was instructed to collect urine over the next 5 hours. The concentration of sugars in urine was measured by high performance thin layer chromatography. After correction of the rhamnose values for urea concentration (the latter was determined in a 1 ml aliquot of urine), the results were expressed as a ratio of the 5 hour urinary excretions of lactulose and rhamnose.¹⁹

STATISTICAL ANALYSIS

Data were evaluated using the Wilcoxon rank sum test (paired measurements), the Mann-Whitney U test (unpaired measurements), the χ^2 test, and linear regression analysis. A *p* value of <0.05 was considered significant. Data are expressed as median values and ranges.

Results

Eighteen of 20 patients completed the study. The two patients who withdrew (numbers 6 and 13) felt they could no longer cope with the programme of evaluations of gastrointestinal function required in the protocol. No significant adverse effects were reported and no significant changes in haematological, biochemical, and electrocardiographic parameters were documented. One scintigraphic assessment of gastric emptying and intestinal transit (in patient 5), one urine collection for the double sugar lactulose/rhamnose permeability test (patient 10) and one faecal fat estimation (in patient 11) were lost. In consequence only 17 paired measurements were used in some cases for the comparison between placebo and loperamide oxide phases of the study.

COMPARISON BETWEEN CONTROL SUBJECTS AND PATIENTS DURING PLACEBO TREATMENT

Table II summarises the results for the patients

and the control subjects during the placebo phase of the study. There was no evidence of small intestinal bacterial overgrowth in the patients – that is, no early rise in breath hydrogen concentrations after oral lactose or lactulose. Both the number of bowel actions per week (assessed by diary) and stool frequency per 3 days (assessed by 3 day faecal collection) were greater in the patients than in the control group ($p < 0.001$). There was no significant difference in stool weight. Except for the frequency of bowel actions, there was no difference in gastrointestinal symptoms between the patients and controls. Bile acid absorption was considerably reduced in the patients ($p < 0.001$), but there was no significant difference between the two groups in vitamin B12 absorption. Faecal fat excretion was less in the patients ($p < 0.01$). Dietary intake of dairy products was lower ($p < 0.02$) and fat intake also tended to be less ($p = 0.09$) in the patients. Ten patients had lactose malabsorption, compared with two of the control subjects ($p < 0.05$). Of the patients with lactose malabsorption, only two had a history of gastrointestinal intolerance to milk or milk products. Despite this, dietary intake of dairy products was less in patients with lactose malabsorption than in the remainder of the group (213 mg (0–4940) *v* 2354 mg (320–8190) $p < 0.05$). Gastrointestinal symptoms after the lactose load were reported by four patients. There was no significant difference in gastric emptying between the two groups, but small intestinal transit ($p < 0.001$) and whole gut transit ($p < 0.05$) were faster in the patients than in the control subjects. There was no significant difference in intestinal permeability between the two groups. In the control group there was a significant correlation ($r > 0.48$, $p < 0.05$) between bile acid absorption and whole gut transit (first radio-opaque marker and 50% markers). In the patients, stool frequency per 3 days was inversely related to bile acid absorption ($r = -0.49$, $p < 0.05$). Otherwise there were no significant relationships between the frequency of bowel actions or stool weight and other parameters of gastrointestinal function in either the patients or the control subjects.

TABLE III Results in patients during the placebo and loperamide phases

Parameter	Placebo	Loperamide oxide	<i>p</i> Value
No of subjects	18	18	
Gastrointestinal symptoms:			
Score	0 (0–3)	0 (0–3)	NS
Bowel actions/wk	19 (9–53)	13.5 (6–39)	<0.001
Stool frequency/3d	7 (2–14)	5 (1–10)	<0.05
Stool wt/3d (g)	450 (186–1275)	260 (63–1170)	<0.01
Absorption:			
SeHCAT (%)	3.3 (0.0–45.7)	20.5 (0.0–65.4)	<0.01
⁵⁸ Co Vit B12 (%)	74.3 (45.1–100)	62.8 (37.7–90.9)	<0.05
Faecal fat (mmol/3d)	33 (11–65)	33 (9–68)	NS
Lactose malabsorption (no)	10	7	NS
Gastrointestinal transit; gastric emptying:			
Lag phase (min)	0.5 (0.5–3.5)	0.5 (0.5–9.5)	NS
50% emptying (min)	55 (1–160)	39 (1–135)	<0.01
Small intestinal transit:			
Start colonic filling (min)	29 (14–73)	37.5 (14–135)	<0.01
50% colonic filling (min)	125 (83–208)	164 (83–269)	<0.001
Small intestinal transit (min)	28 (14–68)	37 (13–134)	<0.01
Small intestinal residence (AUC)	27.4 (18.6–46.8)	41.8 (26.4–62.5)	<0.001
Whole gut transit:			
First marker (h)	21.5 (6–45)	28.5 (10.5–72)	<0.01
50% markers (h)	28.5 (10–72)	58.5 (10.5–72)	<0.05
Intestinal permeability:			
⁵¹ Cr EDTA (%)	1.99 (0.091–8.25)	2.70 (0.16–6.8)	<0.01
Lactulose (mmol/l)	0.60 (0.04–9.8)	0.41 (0.07–9.83)	NS
Rhamnose (mmol/l)	1.91 (0.23–52.2)	2.60 (0.54–21.3)	NS
Lactulose/rhamnose (ratio)	0.06 (0.03–0.25)	0.06 (0.01–0.28)	NS

Data are median values and ranges (analysis by Wilcoxon test).

EFFECTS OF LOPERAMIDE OXIDE

Table III summarises the results during the placebo and loperamide oxide phases of the study. Loperamide oxide decreased stool frequency ($p < 0.001$) and weight ($p < 0.01$). After treatment with loperamide oxide the number of bowel actions was still greater in the patients than in the control subjects ($p < 0.05$) but the stool weight was less ($p < 0.01$) (Table IV). Bile acid absorption was increased appreciably by loperamide oxide ($p < 0.01$) (Figure) and, after treatment, was not significantly different from values in the control group (Table IV). Somewhat surprisingly, treatment with loperamide oxide was associated with a small but significant decrease ($p < 0.05$) in vitamin B12 absorption. Loperamide oxide did not affect faecal fat excretion, but during treatment with this drug there was an inverse relationship between bile acid absorption and faecal fat excretion ($r = -0.63$, $p < 0.01$). There was no difference between the

TABLE IV Results in patients during treatment with loperamide oxide and control subjects

Parameter	Control	Loperamide oxide	p Value
No of subjects	18	18	
Gastrointestinal symptoms:			
Score	0 (0-1)	0 (0-3)	NS
Bowel actions/wk	8 (3-14)	13.5 (6-39)	<0.05
Stool frequency/3d	4 (2-10)	5 (1-10)	<0.05
Stool wt/3d (g)	507 (308-1190)	260 (63-1170)	<0.01
Absorption:			
SeHCAT (%)	22.8 (9.2-63.6)	20.5 (0-65.4)	NS
⁵⁸ Co Vit B12 (%)	81.4 (29.4-98.9)	62.8 (37.7-90.9)	<0.01
Faecal fat (mmol/3d)	53 (20-80)	35 (9-68)	<0.05
Lactose malabsorption (no)	2	7	NS
Gastrointestinal transit; gastric emptying:			
Lag phase (min)	0.5 (0.5-7.5)	0.5 (0.5-9.5)	NS
50% emptying (min)	65 (27-99)	39 (1-135)	<0.05
Small intestinal transit:			
Start colonic filling (min)	57 (23-117)	37.5 (14-135)	NS
50% colonic filling (min)	178 (88-295)	164 (83-269)	NS
Small intestinal transit (min)	52 (22-114)	37 (13-134)	NS
Small intestinal residence (AUC)	39.2 (23.2-57.7)	41.8 (26.4-62.5)	NS
Whole gut transit:			
First marker (h)	26.5 (6.5-48)	28.5 (10.5-72)	NS
50% markers (h)	32.5 (17.5-71)	58.5 (10.5-72)	NS
Intestinal permeability:			
⁵¹ Cr EDTA (%)	1.49 (0.7-4.06)	2.70 (0.16-6.8)	<0.05
Lactulose (mmol/l)	0.93 (0.14-16.3)	0.41 (0.07-9.83)	NS
Rhamnose (mmol/l)	1.85 (0.33-48.3)	2.60 (0.54-21.3)	NS
Lactulose/rhamnose (ratio)	0.095 (0.04-0.29)	0.06 (0.01-0.28)	NS

Data are median values and ranges (analysis by Mann-Whitney U test).

two groups in the lag phase, but the time for 50% gastric emptying was less during treatment with loperamide oxide ($p < 0.01$) and gastric emptying was faster in patients after treatment with loperamide oxide ($p < 0.05$) than in control subjects (Table IV). In contrast, loperamide oxide delayed both small intestinal ($p < 0.01$) and whole gut ($p < 0.01$ first marker, $p < 0.05$ 50% markers) transit. During treatment with loperamide oxide, small intestinal transit and whole gut transit were not significantly different from the control group (Table IV). There were significant relationships between stool weight and both whole gut transit ($r = -0.58$, $p < 0.01$) and stool frequency ($r = 0.45$, $p < 0.05$) during treatment with loperamide oxide. Intestinal permeability, as assessed by the ⁵¹Cr EDTA test, was greater ($p < 0.01$) after treatment loperamide oxide but there was no difference in the absorption of lactulose/rhamnose (Table III). ⁵¹Cr EDTA absorption was related to small bowel residence during both the placebo and loperamide oxide phases ($r > 0.45$, $p < 0.05$).

Absorption of bile acid in control subjects and patients with radiation enteritis during treatment with placebo and loperamide oxide. Data are shown as median values and interquartile ranges.

Discussion

During abdominal or pelvic irradiation, or both, acute radiation enteritis, manifest as diarrhoea with or without abdominal cramps, is almost inevitable.^{1,6} The prevalence of chronic radiation enteritis, defined as the persistence of symptoms beyond 3 months of the completion of radiation treatment, is, however, uncertain.¹ Several retrospective surgical series suggest that the incidence of 'significant' damage is only 5-15%.^{20,21} These studies have considerable limitations, however. In particular, they do not include patients who died or were lost to follow up in the prolonged interval between treatment and the onset of symptoms. In contrast, a sustained increase in bowel frequency was noted in 12 of 17 unselected women who had received pelvic radiotherapy for gynaecological malignancy 1-26 years previously.² It therefore seems probable that the incidence of chronic radiation enteritis has been generally underestimated (and may be more than 50%), that increased bowel frequency is the most frequent symptom of chronic radiation enteritis, and that most patients with this condition do not seek medical help until the occurrence of a severe complication such as stricture, perforation, or anaemia caused by blood loss.¹ There is some evidence that the incidence of radiation bowel disease has increased in recent years as a result of changes in long established techniques.^{3,5} For example, although radium has now been replaced by safer isotopes such as cesium and cobalt, this has also entailed new or modified applicators, altered dose rates, and changes in the number of treatments.

The rectum, sigmoid colon, and terminal ileum seem to be particularly at risk from pelvic radiotherapy.⁴ While the histological features of chronic radiation enteritis, characterised by obliterative endarteritis of the small vessels in the intestinal wall, submucosal oedema, and lymphatic dilatation are well documented,²² there is little information about the pathophysiology of diarrhoea caused by chronic radiation enteritis.¹⁴ It has been suggested that diarrhoea reflects malabsorption because of either infiltration of the mucosa by inflammatory cells and luminal narrowing of the submucosal arterioles,²³ or intestinal bacterial overgrowth.⁴ The possibility that abnormalities in intestinal motor function may be important has also been recognised.^{6,24} In the first comprehensive study of intestinal function in patients with diarrhoea caused by chronic radiation enteritis, we have shown a high prevalence of abnormalities in intestinal transit and absorption. Both small intestinal and whole gut (mainly colonic) transit, were faster in the patients than the control subjects. Bile acid absorption was reduced in many of the patients (although vitamin B12 absorption was usually normal), and 10 patients had malabsorption of lactose. All of these factors may theoretically contribute to diarrhoea. These observations were not the result of intestinal stricture or bacterial overgrowth. The relatively small difference in median age between the patients and the control subjects is unlikely to be important. The observation that despite increased stool frequency, stool weight was not greater in the patients is likely to reflect dietary

changes, which inevitably occur in patients with a long history of diarrhoea. Intake of dairy products was less in the patients and probably contributed to the normal faecal fat excretion. It is also possible that in some patients concurrent radiation proctitis caused rectal irritability and contributed to a stool weight that was lower than would be predicted from stool frequency.

The SeHCAT test has made intestinal bile acid malabsorption much more easy to detect.^{25,26} A high prevalence of bile acid malabsorption has been reported in patients with otherwise unexplained diarrhoea^{26,27} and it has been suggested that this is of pathogenetic importance and predictive of improvement with cholestyramine.²⁶ Our observation of a high prevalence of bile acid malabsorption in patients with chronic radiation enteritis is consistent with the results of a previous study.⁴ While vitamin B12 malabsorption has been shown in some patients,⁴ it is recognised that bile acid absorption is a more sensitive test of terminal ileal function than vitamin B12 absorption.²⁸ The reduced bile acid absorption is likely to reflect damage to the terminal ileal mucosa. It should, however, be recognised that more rapid intestinal transit, by reducing the time available for absorption, could contribute to decreased bile acid absorption and diarrhoea.^{6,27,29} In particular, the terminal ileum seems to have an important role in the regulation of small intestinal transit.³⁰

The lactose malabsorption shown in 10 patients probably reflects mucosal damage, as small intestinal bacterial overgrowth was essentially excluded and all of the patients were white. A high prevalence of lactose malabsorption has been reported previously in patients with chronic radiation enteritis who required parenteral nutrition.³¹ The observation that lactose malabsorption is a common long term effect of abdominal or pelvic irradiation, or both, is important and consistent with the findings of a prospective study conducted by our group which suggests that mucosal damage in acute radiation enteritis does not resolve in many patients.⁷ It is not surprising that a history of milk intolerance was seldom obtained in patients with lactose malabsorption, although dietary intake of dairy products was reduced.¹¹

We have shown for the first time that small intestinal and whole gut transit is faster in patients with chronic radiation enteritis. Both single large doses and fractionated doses of radiation have been shown to alter small intestinal motility in animals.^{24,32} Fractionated doses of abdominal radiation increase the frequency of giant migrating contractions and retrograde giant contractions.²⁴ We and others have reported that both small intestinal and total gut transit is faster in acute radiation enteritis.^{7,33} Although there is unequivocal evidence of damage to the intestinal smooth muscle in chronic radiation enteritis,³⁴ we are unaware of any studies of intestinal motor function in chronic radiation enteritis in either animals or humans.

Medical therapy of diarrhoea caused by chronic radiation enteritis has been largely empirical and there have been no adequate controlled studies.¹ Antidiarrhoeal agents, broad spectrum antibiotics, cholestyramine, sulpha-

salazine, and oral corticosteroids have all been used^{3,35,36} but anecdotal experience suggests that satisfactory control of diarrhoea is rarely achieved. Most series have focused on surgical approaches to complications such as stricture and fistula formation. The results of our study indicate that loperamide-N-oxide is effective in the treatment of diarrhoea associated with chronic radiation enteritis.

Loperamide-N-oxide is a peripheral opiate agonist precursor which is converted to loperamide in the intestinal lumen³⁷ and liver.³⁸ Loperamide-N-oxide is itself inactive and has negligible affinity for opiate receptors.³⁹ Plasma concentrations of loperamide after oral administration of loperamide-oxide are twofold lower than the equivalent oral doses of loperamide,⁴⁰ resulting in a twofold increase in the already high safety margin of loperamide.^{40,41} At the same time anti-diarrhoeal efficacy is maintained, since a dose of even 1 mg has been shown to be effective in a randomised double blind study of acute diarrhoea in adults.⁴² As a result of the gradual activation of loperamide oxide, associated with lessened absorption of loperamide into the systemic circulation, it has been suggested that the incidence of adverse effects such as constipation may be less.⁴¹

Previous studies^{43,44} which suggest that loperamide may be effective in the treatment of diarrhoea associated with acute radiation enteritis provide no insights into the mechanisms of action, as only symptoms were evaluated. Other studies indicate that loperamide may prolong intestinal transit, normalise intestinal fluid and electrolyte movement, and increase anal sphincter tone.^{45–48} Loperamide treatment of diarrhoea associated with chronic radiation enteritis was associated with significant changes in stool frequency and volume, gastrointestinal transit, intestinal absorption, and permeability. Stool frequency and volume decreased and bile acid absorption increased after treatment. We are unable to explain why vitamin B12 absorption decreased during treatment with loperamide oxide, but can only comment that the magnitude of the change was relatively small. Loperamide oxide increased the rate of gastric emptying but slowed both small intestinal and whole gut transit. Intestinal permeability to ⁵¹Cr EDTA but not lactulose/rhamnose was increased by loperamide oxide. The beneficial effects of the drug on stool frequency, bile acid absorption, and intestinal permeability are likely to reflect the slowing of small intestinal and colonic transit.⁴⁵ The fact that permeability, as evaluated by the double sugar test, was not increased is consistent with this hypothesis, as results of this test are independent of intestinal transit.⁴⁹ An effect of loperamide oxide on intestinal secretion cannot be excluded as this was not examined.⁴⁴ The faster gastric emptying after treatment is not unexpected.⁵⁰ This effect is likely to reflect the absence of central opiate properties of loperamide compared with other opiates such as morphine which slow gastric emptying. Although most of our patients had minimal upper gastrointestinal symptoms and normal gastric emptying, the effect of loperamide on gastric emptying may be beneficial in some patients with chronic

radiation enteritis, as chronic gastroparesis is a recognised sequel to abdominal irradiation.⁵¹

We thank Miss T Piscioneri for typing the manuscript. This study was supported by the National Health and Medical Research Council of Australia and Janssen Pharmaceutica.

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