SHORT REPORTS

Loperamide, diphenoxylate, and codeine phosphate in chronic diarrhoea

Loperamide, diphenoxylate, and codeine phosphate are commonly used to treat chronic diarrhoea. There have been only two controlled studies that compare loperamide with diphenoxylate in patients with chronic diarrhoea,[1 2] and there has been no comparison of loperamide with codeine phosphate for this condition.

Patients, methods, and results

Eleven patients with chronic diarrhoea participated in this outpatient trial: nine were receiving maintenance treatment with codeine phosphate (mean dose 128 mg/day) and two with loperamide (8 mg/day). The causes of the diarrhoea were ileal resection and right hemicolectomy (six patients), colectomy and ileorectal anastomosis (two patients), and unknown in three patients. The patients had had no operations for at least one year and showed no evidence of active inflammatory bowel disease.

All antidiarrhoeal drugs were stopped, and the patients received four successive courses of treatment, each lasting a fortnight. The treatment was double-blind and given in a predetermined random order. The patients were advised to take sufficient capsules in divided doses to control their diarrhoea. The capsules looked identical and contained either loperamide 2 mg (as two separate courses, loperamide 1 and loperamide 2), diphenoxylate 5 mg with atropine sulphate 0·05 mg, or codeine phosphate 30 mg. At the end of each course the patients returned unused capsules, a completed diary card, and a questionnaire. This study was approved by the hospital ethical committee, and each patient gave written consent.

The three drugs were well tolerated, and no serious side effect was reported. The table shows the mean daily bowel activity, the stool consistency, and the mean number of capsules taken during the last 10 days of each course of treatment. Although the total number of capsules taken during each course of treatment was almost identical, there was considerable variation in day-to-day consumption. No patient showed any preference for a particular drug.

Daily bowel actions, stool consistency, number of capsules taken, and dose taken in 11 patients with chronic diarrhoea receiving four different courses of treatment. Results given as means ± SEM or as percentages in parentheses

	Drug taken			
	Loperamide 1	Loperamide 2	Diphenoxylate	Codeine phosphate
Bowel actions/day	3·9 ± 1·2	3·9 ± 1·1	3·9 ± 1·1	3·9 ± 1·1
Stool consistency (%)				
Hard	(3)	(3)	(3)	(3)
Formed	(24)	(25)	(24)	(25)
Loose	(73)	(72)	(73)	(72)
Capsules/day	3·5 ± 0·5	3·5 ± 0·5	3·5 ± 0·5	3·6 ± 0·5
Dose/day (mg)	7·0	7·0	17·5	109·0

Comment

This trial did not include a course of placebo treatment, since it was considered unethical to withhold treatment from outpatients with chronic diarrhoea.

Pelemans and Vantrappen[1] found that an optimal dose of loperamide (6·9 mg/day) was better than an optimal dose of diphenoxylate (17·7 mg/day), but Verhaegen *et al*[2] found no significant difference in a cross-over trial comparing loperamide (optimal dose 10 mg/day) and diphenoxylate (15 mg/day). Cowen and Campbell,[3] in a cross-over study using fixed doses of diphenoxylate (15 mg/day) and codeine phosphate (45 mg/day), showed that the two drugs were equally more effective than placebo.

Our present study shows that for treating chronic diarrhoea codeine phosphate 30 mg is equivalent to loperamide 2 mg (1 capsule of Imodium) or diphenoxylate 5 mg (two tablets of Lomotil or Reasec). Codeine phosphate and diphenoxylate are dangerous when taken in excess, especially by children, because both have a central narcotic effect.[4 5] If there is no hazard of addiction or accidental overdosage, codeine phosphate is the best drug for chronic diarrhoea because it is the cheapest. If the patient has small children or a history of mental illness, however, loperamide appears to be the drug of choice, since it has no apparent narcotic activity.[2]

The authors thank Janssen Pharmaceuticals who provided loperamide, diphenoxylate, and codeine phosphate.

[1] Pelemans W, Vantrappen G. A double-blind cross-over comparison of loperamide with diphenoxylate in the symptomatic treatment of chronic diarrhoea. *Gastroenterology* 1976;**70**:1030-4.
[2] Verhaegen H, De Cree J, Schuermans V. Loperamide, a novel type of anti-diarrhoea agent: part 7. *Arzneim Forsch* 1974;**24**:1657-60.
[3] Cowen AE, Campbell CB. Symptomatic therapy for chronic diarrhoea. A comparison of the effects of codeine phosphate and diphenoxylate. *Med J Aust* 1973;**1**:842-3.
[4] von Muhlendahl KE, Scherf-Rahne B, Krienke EG, Baukloh G. Codeine intoxication in childhood. *Lancet* 1976;ii:303-4.
[5] Penfold D, Volans GN. Overdose of Lomotil. *Br Med J* 1977;ii:1401-2.

(*Accepted 29 November 1979*)

Gastrointestinal Laboratory, Rayne Institute, St Thomas's Hospital, London SE1 7EH
C D SHEE, MB, MRCP, research registrar
R E POUNDER, MD, MRCP, senior medical registrar

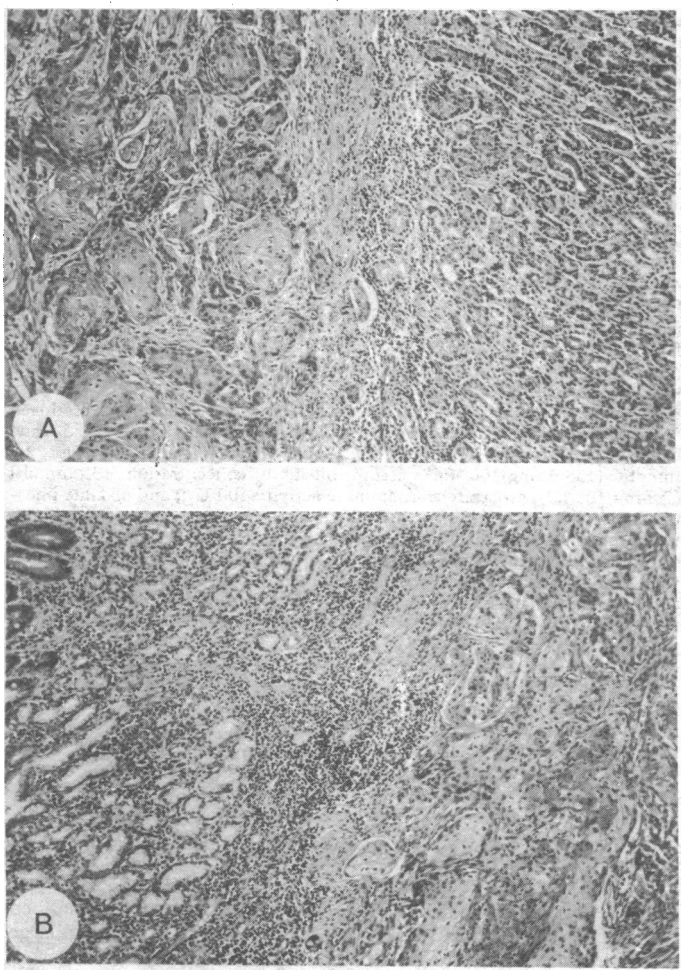
Cyclophosphamide and pure squamous-cell carcinoma of the stomach

Under 40 cases of pure squamous-cell carcinoma of the stomach have been reported worldwide.[1] We describe two patients who developed this rare tumour during long-term treatment with cyclophosphamide.

Case reports

Case 1—In 1974 a previously fit 64-year-old seaman developed progressively more severe backache. On investigation he was found to have multiple myeloma, with lytic lesions in the L3 and L5 vertebrae and a bone marrow aspirate containing 36% atypical plasma cells. The erythrocyte sedimentation rate was 44 mm in the first hour (Westergren), but the results of serum immunoelectrophoresis were normal and Bence-Jones proteinuria was not detected. The investigations with normal results included blood and platelet counts, urine microscopy, serum proteins, urea and electrolytes, creatinine, calcium, liver function tests, intravenous urography, and chest radiography. The patient was treated initially with local radiotherapy to the lumbar spine and then put on cyclophosphamide, 100 mg daily. His blood count was monitored at two-weekly intervals but at no time did he develop haematopoietic toxicity. He remained well until December 1978, when he passed a melaena stool. Barium meal examination showed a large gastric tumour extending from the midpoint of the lesser curve to the pylorus. At laparotomy no sign of extragastric spread was found even though the tumour had penetrated to the serosal surface of the lesser curvature. A radical subtotal gastrectomy was performed. The specimen of resected stomach measured 13 cm along the lesser curve and 10 cm along the greater curve. A large nodular tumour 6 × 4 cm extended from 5 cm distal to the cardiac end of the specimen to within 1 cm of the pyloric sphincter. Thirteen separate sections through the tumour were examined histologically. Each section showed a well-differentiated, keratinising pure squamous-cell carcinoma (fig). No metastatic lymphatic spread was found. The patient made an uneventful recovery and is at present well. The total amount of cyclophosphamide he had taken was 165 g.

Case 2—A 49-year-old woman, a factory worker, had subacute lupus erythematosus diagnosed in January 1972 and was treated initially with prednisone. Three months later she complained of severe indigestion and was found on barium-meal examination to have a small lesser-curve ulcer. Gastroscopy and biopsy showed the ulcer to be benign. The prednisone was discontinued, being replaced by cyclophosphamide, 150 mg daily. Gastroscopy was repeated in August 1972 and the ulcer was found to have healed. In 1975 the patient presented with a haematemesis and melaena requiring emergency surgery. At operation a large ulcerating gastric carcinoma was found to extend from 10 cm distal to the cardia along the lesser curve of the stomach to the pyloric antrum.



Sections of pure squamous-cell gastric carcinomas, ×10: case 1 (a); case 2 (b). (Original magnification.)

A subtotal gastrectomy was performed. On microscopy six sections taken from different sites within the tumour were found to be identical, consisting of pure squamous-cell carcinoma devoid of any glandular elements (fig). The total dose of cyclophosphamide the patient had received was 140 g.

Comment

The carcinogenic potential of cyclophosphamide is well known.[2] Ten malignant tumours have been reported in patients prescribed cyclophosphamide for non-malignant conditions and 22 second primary tumours in patients treated with cyclophosphamide for a primary malignancy. This is the first report of an association between the development of squamous-cell gastric carcinoma and the long-term use of this drug. Conceivably the gastric cancers that developed in these patients were simply the result of intercurrent predisposing factors and not a side effect of the drug. In that case, however, why should both patients have developed the rare pure squamous-cell gastric carcinoma? We suggest that both cases represent further examples of cyclophosphamide-induced malignancy.

We thank Mr D P B Turner, FRCS, and Mr John Campbell, FRCS, for permitting us to report case 1.

[1] Won OH, Farman J, Krishnan MN, Iyer SK, Vuletin JC. Squamous cell carcinoma of the stomach. *Amer J Gastroenterol* 1978;69:594-8.
[2] *I A R C Monogr Eva Carcinog Risk Chem Man* 1975;9:135-56.

(*Accepted 20 November 1979*)

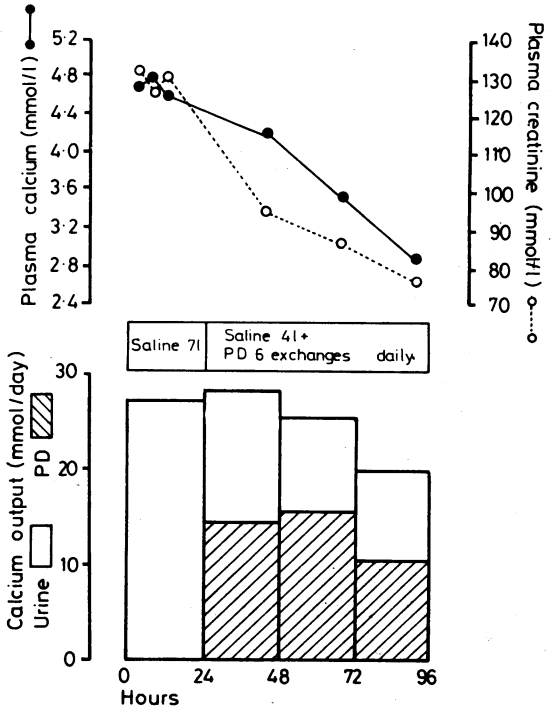
Departments of Surgery and Pathology, Broadgreen Hospital, Liverpool L14 3LB
G A McLOUGHLIN, FRCS, senior surgical registrar
D J CAVE-BIGLEY, FRCS, surgical registrar
V TAGORE, MRCPATH, senior registrar pathology
N KIRKHAM, MB, registrar pathology

Peritoneal dialysis in the management of severe hypercalcaemia

Severe hypercalcaemia often presents as an acute emergency without an obvious cause. Initial management aims to lower plasma calcium until the cause of the hypercalcaemia is established. Renal failure is usually present, and treatment by peritoneal dialysis to reduce plasma calcium and to improve uraemia has obvious advantages over present standard treatments. Nevertheless, its use has not become established since most commercially prepared dialysis fluids contain calcium. Travenol Laboratories have recently produced a 3-l parenteral infusion container into which solutions of any composition can be introduced. We have used it for peritoneal dialysis with calcium-free dialysate in a patient with severe resorptive hypercalcaemia. Our biochemical methods have been described.[1]

Case report

A 46-year-old woman was admitted acutely in an unresponsive state. Her history, obtained from relatives, was of dysphagia, weight loss, nausea, and haemoptysis of four weeks' duration. She was feverish (38·6°C), dehydrated, and had a sinus tachycardia and hepatomegaly. Investigation showed a hypochromic, microcytic anaemia of 6·7 g/dl, an erythrocyte sedimentation rate (ESR) of 80 mm in 1st h, and a neutrophil leucocytosis of $25{\cdot}8 \times 10^9$/l ($25\,800/mm^3$). Initial management was directed at probable septicaemia with intravenous fluids and parenteral lincomycin and gentamicin. Investigations were difficult because of the patient's unresponsiveness, but a liver scan showed multiple holes consistent with abscesses or metastases. A biochemical profile indicated severe hypercalcaemia, with plasma calcium 4·68 mmol/l (18·72 mg/100 ml) (normal range 2·22-2·60 mmol/l (8·9-10·4 mg/100 ml)). The patient was then transferred to our care.



Plasma calcium and creatinine concentrations and calcium output during saline infusion and saline infusion and peritoneal dialysis (PD).
Conversion: SI to traditional units—Plasma calcium: 1 mmol/l ≈ 4 mg/100 ml. Plasma creatinine: 1 μmol/l ≈ 0·0113 mg/100 ml. Calcium output: 1 mmol = 40 mg.

Further investigation showed a plasma ionised calcium of 2·38 mmol/l (9·52 mg/100 ml) (normal range 1·13-1·28 mmol/l (4·52-5·12 mg/100 ml)), mild renal failure with a plasma creatinine of 131 μmol/l (1·48 mg/100 ml) (normal range 64-106 μmol/l (0·72-1·19 mg/100 ml)), increased urinary calcium with a fasting urinary Ca:Cr of 0·76 (normal range <0·425), increased urinary hydroxyproline excretion with a fasting OHPr:Cr of