by the generous support of the Scottish Hospital Endowments Research Trust and would have certainly failed were it not for the dedicated assistance of our secretary, Mrs Jenny Stewart.

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(Accepted 20 June 1985)

SHORT REPORTS

Nabilone and prochlorperazine: a useful combination for emesis induced by cytotoxic drugs

The control of emesis induced by cytotoxic drugs remains a major challenge. Our recent experience indicates that the failure rate is high even when patients receive parenteral antiemetic prophylaxis.[1] Further innovation is clearly required, including the development of antiemetic protocols suitable for outpatient use, as chemotherapy without cisplatin is usually administered on an outpatient basis. Nabilone is a synthetic cannabinoid with established antiemetic activity when administered orally, but adverse effects on the central nervous system, such as dysphoria, have limited its widespread application.[2] In clinical studies the phenothiazines reduced the incidence of euphoria associated with delta-9-tetrahydrocannabinol,[3 4] the most active constituent of cannabis. The aim of this study was to investigate whether such an effect occurred when prochlorperazine was added to nabilone.

Patients, methods, and results

Thirty four patients (20 women, 14 men; mean age 55 (range 39-76)) entered the study. Four had received previous chemotherapy and had been refractory to other antiemetics, but the remaining 30 were receiving their first course of chemotherapy. None had been given nabilone, and to our knowledge none had taken cannabis in the past. All were receiving cytotoxic regimens without cisplatin. Patients were randomly assigned using a double blind crossover method to nabilone 2×1 mg capsules combined with prochlorperazine (5 mg) or nabilone and placebo. The first dose was given at 10 pm the night before chemotherapy, and three further doses were given at intervals of 12 hours, although if vomiting did not occur the final dose was omitted. Nausea, vomiting, adverse effects, blood pressure, and pulse were recorded on an inpatient basis for the 24 hours after chemotherapy, and patients assessed control of emesis on a linear analogue scale. Wilcoxon's matched pairs signed ranks test was used to compare these variables and the binomial test to analyse patient preference (if any) for either antiemetic.

Four patients did not complete two courses: three died, and chemotherapy was stopped in one. The table shows the results for all 34 patients. Among the patients who completed the crossover there were no significant differences in nausea, vomiting, appetite, assessment on the linear analogue scale, or adverse effects other than those on the central nervous system, which were significantly less common with the combination ($p < 0.01$). A significant number of patients preferred the combination (15 *v* 1, $p < 0.001$); 14 had no preference. There was no significant relation between the order of administration of the drug and drug preference (Fisher's exact test).

Comment

Nabilone alone, or in combination with prochlorperazine, proved to be a highly effective antiemetic, providing complete control of emesis in a large proportion of our patients receiving cytotoxic regimens of considerable emetogenic potential.[5] Simultaneous administration of the phenothiazine significantly reduced the incidence of adverse effects on the central nervous system related to nabilone, and the patients clearly preferred the combination. Experience with delta-9-tetrahydrocannabinol indicated that the best antiemetic effect was observed in patients developing "highs."[6] Therefore, in this study the trend towards better control of emesis with the combination of antiemetics was reassuring, as we were concerned that if prochlorpera-

Nausea, vomiting, appetite, and side effects after chemotherapy in all patients. (Figures are numbers (%) of patients)

	Nabilone (n = 31)	Nabilone and prochlorperazine (n = 33)
Episodes of vomiting:		
None	23 (74)	28 (85)
1-2	6 (19)	2 (6)
>2	2 (7)	3 (9)
Duration of vomiting (hours):		
None	23 (74)	28 (85)
1-4	5 (16)	4 (12)
4-8	3 (10)	1 (3)
Severity of nausea:		
None	23 (74)	29 (88)
Mild	6 (19)	4 (12)
Moderate	2 (7)	
Severe		
Duration of nausea (hours):		
None	23 (74)	27 (88)
1-4	4 (13)	3 (9)
4-8	1 (3)	1 (3)
>8	3 (10)	
Appetite:		
Normal	19 (61)	23 (70)
Decreased	12 (39)	10 (30)
Sedation:		
None	4 (13)	3 (9)
Mild	15 (48)	17 (52)
Moderate	9 (29)	10 (30)
Severe	3 (10)	3 (9)
Dizziness:		
None	12 (39)	14 (42)
Mild	15 (48)	13 (39)
Moderate	1 (3)	5 (16)
Severe	3 (10)	1 (3)
Dry mouth:		
None	6 (19)	4 (12)
Mild	11 (36)	10 (30)
Moderate	9 (29)	14 (42)
Severe	5 (16)	5 (16)
Postural hypotension	2 (7)	1 (3)
Adverse effects on central nervous system:		
Visual hallucinations	4 (13)	1 (3)
Euphoria	2* (7)	
Dysphoria	7 (23)	1 (3)
Disorientation	1† (3)	

*Both had hallucinations.
†Also dysphoria.

zine successfully reduced the incidence of dysphoric reactions it might also antagonise the antiemetic effect of nabilone. The incidences of other side effects were similar in both treatment arms; sedation and dryness of the mouth occurred most commonly and generally were not too troublesome. Indeed, we suspect that with moderately emetogenic cytotoxic regimens[5] the occurrence of these side effects could be reduced by using a lower dose of nabilone (1 mg twice daily) without necessarily compromising the control of emesis.

Nabilone and prochlorperazine are a good oral antiemetic combination suitable for use with outpatient chemotherapy, but because they are associated with a small incidence of adverse effects on the central nervous system the first course of treatment should be given under inpatient supervision.

We thank Eli Lilly for financial support and Miss A Penrice, our secretary.

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(*Accepted 4 July 1985*)

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Gastrointestinal haemorrhage complicating Wegener's granulomatosis

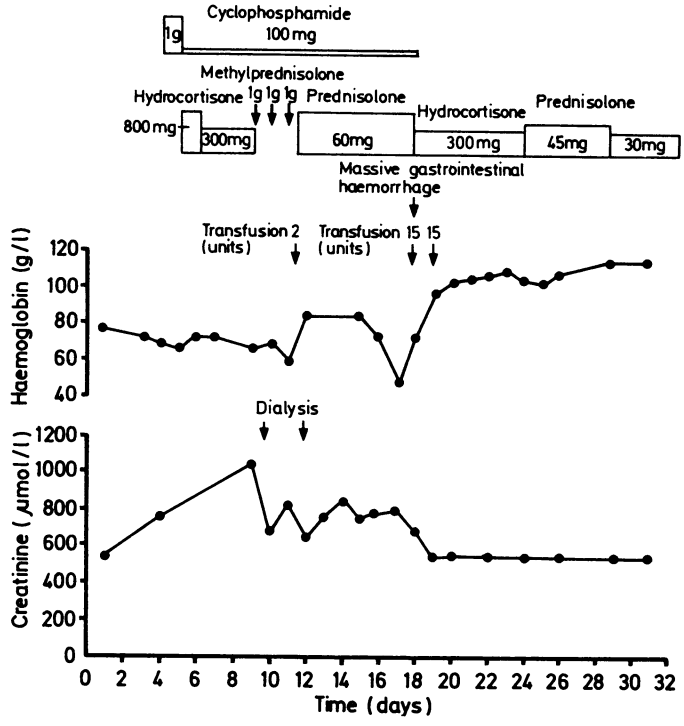
Wegener's granulomatosis is a vasculitic disorder with distinct clinical and histological features, showing considerable overlap with other diseases within the range of systemic vasculitis.[1] Classically, pulmonary disease and nasopharyngeal symptoms are universal, with a severe necrotising glomerulonephritis occurring in 80% of patients and other systems being affected less commonly.[2] We report on a patient with clinical Wegener's granulomatosis who developed severe gastrointestinal and intraperitoneal haemorrhage. Such a complication has not been reported previously.

Case report

A 46 year old man presented to the ear, nose, and throat department with a persistent nasal discharge and necrotic ulcers on his buccal mucosa and tongue; biopsy specimens of these were not obtained. He had a six month history of general malaise and weight loss and recent symptoms of polyarthralgia, iritis, and a vasculitic rash on his legs; he had received ibuprofen for two weeks before admission. A chest *x* ray film showed a cavitating lesion in the right upper lobe, and laboratory investigation showed a normochromic normocytic anaemia with renal failure: haemoglobin concentration was 79 g/l; erythrocyte sedimentation rate 116 mm in the first hour; urea concentration 35·7 mmol/l (214 mg/100 ml); and creatinine concentration 540 μmol/l (6·1 mg/100 ml). Treatment with cyclophosphamide and hydrocortisone greatly improved his arthralgia, vasculitic rash, and general condition, but his renal function continued to deteriorate and he required haemodialysis. Renal biopsy showed diffuse necrotising crescentic glomerulonephritis with focal segmental granular deposits of IgG, IgM, C3, and C4. Further immunosuppression with pulsed doses of 1 g methylprednisolone and oral prednisolone (60 mg daily) resulted in improved renal function.

Twelve days after admission, when his clinical condition had improved and his erythrocyte sedimentation rate was 27 mm in the first hour, he suffered a massive gastrointestinal haemorrhage. Mesenteric angiography showed a bleeding point in the distal small bowel. At laparotomy several inflammatory areas were recognisable on the serosal surface of the distal ileum. One metre of distal ileum was resected, which contained nine punched out mucosal ulcers corresponding to the areas of serosal inflammation. The most distal of these bore adherent thrombus.

Histological examination showed active arteritis with fibrinoid necrosis and sparse perivascular lymphocytic infiltration. Postoperatively he suffered an intraperitoneal haemorrhage, the source of which could not be located at re-exploration six hours later. Splenectomy was performed because of a persistent oozing around the spleen, which was grossly abnormal and wrapped in omentum. A small tear was found at the upper pole of the spleen, and histological examination showed multiple infarcts up to 1 cm diameter with patchy vasculitis and thrombosis of medium sized arteries. Further haemorrhage was controlled by packing the splenic bed. During these procedures 30 units of blood were transfused. He made a good postoperative recovery with impaired but stable renal function (figure).



Effect of treatment on serum creatinine concentration, and relation of gastrointestinal haemorrhage to recovery of renal function.

Conversion: SI to traditional units—Creatinine: 1 μmol/l ≈ 11·3 μg/100 ml.

Comment

Over half of the patients with classical polyarteritis nodosa experience abdominal pain, and 44% of these have gastrointestinal haemorrhage.[3] Gastrointestinal complications are rare in Wegener's granulomatosis, being found in four of 36 patients studied by Camilleri *et al*,[3] only one of whom had poorly documented gastrointestinal haemorrhage. Pinching *et al* reported bleeding from a duodenal ulcer in a patient with Wegener's granulomatosis, although they believed this to be related to steroid treatment as it occurred when the disease was quiescent.[4] This assumption may be false as bleeding occurred in our patient when clinical and laboratory evidence indicated a response to immunosuppression while histological examination of the gut and spleen showed active arteritis with intravascular thrombus. Our case parallels a report of cortical blindness, presumably thrombotic, occurring in a patient with Wegener's granulomatosis at a time when renal function was improving.[5] Such observations suggest that different mechanisms have a role in the early systemic manifestations of the disease, which may respond rapidly to immunosuppression, and in the later thrombotic complications secondary to endothelial damage, in which antiplatelet agents and prostacyclin analogues might be of benefit.

We would like to thank Dr D A Jones, consultant physician, Grimsby District General Hospital, for referring the patient.