topical steroids. Examination showed a brownish-red, sharply margined scaly plaque overlying the knuckles and proximal phalanges, candidal cheilitis, a vulval rash, and a non-healing sore on the right foot.

Her lifelong epilepsy had necessitated treatment with phenobarbitone, carbamazepine, and phenytoin. Substitution of high dose sodium valproate for phenytoin in 1981 had induced dose related vomiting with a weight loss of 25.4 kg (original weight 90 kg), diffuse alopecia, and dry skin. After seven months sodium valproate had been changed to phenytoin, but the weight loss continued with dysgeusia, refusal of food, vomiting, and alternating diarrhoea and constipation. No organic cause had been found, and behavioural problems had necessitated psychiatric referral.

Zinc deficiency was diagnosed clinically. Serum zinc concentration was $8.2 \mu\text{mol/l}$ ($54 \mu\text{g}/100 \text{ ml}$) (laboratory normal $12.7\text{--}20 \mu\text{mol/l}$ ($83\text{--}131 \mu\text{g}/100 \text{ ml}$)). Serum albumin concentration was not measured at the time of diagnosis but had been normal throughout 1982-3 until two months previously. All signs and symptoms responded to oral zinc sulphate within two weeks. Relapse did not occur despite continuing treatment with phenytoin and carbamazepine.

CASE 2

In August 1983 a mentally subnormal epileptic man aged 28 presented with a one month history of a condition similar to seborrhoeic dermatitis of the face and neck, angular cheilitis, and a brownish-red, well demarcated scaly rash on the dorsum of both hands overlying the knuckles (figure). His lifelong

Typical lesions of acrodermatitis enteropathica with scaly rash similar to seborrhoea around nasolabial folds, chin, and neck associated with candidal angular cheilitis. Rash on dorsum of left hand appeared over bony prominences of metacarpophalangeal and proximal interphalangeal joints.

refractory epilepsy had been treated with phenobarbitone, phenytoin, and carbamazepine until 1979 when high dose sodium valproate had been substituted for phenytoin. In 1982 he had developed severe ulcerative colitis that was difficult to control because of poor compliance, and he had required several hospital admissions.

In 1983, despite intensive inpatient treatment, diarrhoea was uncontrollable and the rash, typical of acrodermatitis enteropathica, developed. Serum zinc concentration was $3 \mu\text{mol/l}$ ($20 \mu\text{g}/100 \text{ ml}$) and serum albumin concentration 32 g/l . After two weeks' treatment with intravenous zinc sulphate and parenteral nutrition the rash had resolved and the serum zinc concentration was normal. His recovery was complicated by septicaemia due to *Staphylococcus aureus*, but his ulcerative colitis became well controlled. Sodium valproate was continued for his epilepsy with oral zinc supplements; relapse did not occur.

Comment

Diagnosis of zinc deficiency is difficult and usually rests on the clinical picture and response to zinc treatment. No ideal laboratory tests are yet available, and measurement of the serum zinc concentration is probably the most useful. Whether a correction should be made for serum albumin concentration is debatable.

Lowered serum zinc concentrations during anticonvulsant treatment have been reported by several workers,² but others have found concentrations to be unchanged.³ Chelation of zinc by phenytoin⁴ and sodium valproate⁵ in the gut is thought to occur, producing increased uptake but increased urinary excretion of zinc. Binding of zinc in the serum may decrease its free availability.

As zinc deficiency is rare and anticonvulsant treatment common we postulate that the deficiency in these cases occurred as a result of chelation of zinc by sodium valproate and possibly phenytoin in combination with malabsorption. In case 1 the malabsorption was initiated by sodium valproate, and presumably as symptoms of zinc deficiency developed the process became self perpetuating. In case 2 malabsorption occurred as a result of ulcerative colitis and zinc deficiency undoubtedly accounted for failure to control the colitis.

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Whiston Hospital, Prescott, Merseyside

M S LEWIS-JONES, MB, MRCP, registrar in dermatology
S EVANS, MD, consultant dermatologist
M A CULSHAW, MPHARM, MPS, staff pharmacist

Correspondence to: Dr M S Lewis-Jones, Department of Dermatology, Royal Liverpool Hospital, Liverpool L69 3BX.

Randomised trial of intravenous high dose metoclopramide and intramuscular chlorpromazine in controlling nausea and vomiting induced by cytotoxic drugs

High dose metoclopramide given by intermittent intravenous infusion is one of the best antiemetics for the treatment of emesis induced by cytotoxic drugs.¹ This method of administration, however, produces fluctuating plasma concentrations and can lead to accumulation of the drug with the risk of toxicity.² A continuous intravenous infusion overcomes this fluctuation and, as the antiemetic effect of metoclopramide is related to its plasma concentration,³ may also enhance the drug's antiemetic properties. Chlorpromazine is a widely used antiemetic and has not been compared with high dose metoclopramide in the control of emesis. It is effective when administered intramuscularly and thus presents less of a logistic problem in delivery than high dose metoclopramide.

Patients, methods, and results

Ninety five patients (52 women, 43 men; mean age 49) received their first course of chemotherapy, which consisted of regimens containing cisplatin or cisplatin analogues in 43 and regimens without cisplatin in 52. Patients were randomly assigned either antiemetic by a double blind, double dummy technique. Metoclopramide was given as a 50 mg loading dose intravenously 30 minutes before chemotherapy, followed by a 12 hour intravenous infusion of 5 mg/kg in 500 ml physiological saline. Chlorpromazine 25 mg (1 ml) was given intramuscularly every four hours for 12 hours, beginning with the chemotherapy. Nausea and vomiting were recorded for the 24 hours after the end of chemotherapy, and patients assessed control of emesis on a linear

analogue scale. The Wilcoxon matched pairs signed ranks test was used to compare these variables and the binomial test to analyse patient preference (if any) for either antiemetic.

Ten patients given cisplatin and 11 of the others did not complete two courses because of death (10), violation of the protocol (seven), stopping chemotherapy (two), refusal of intramuscular injections (one), and a dystonic reaction (one). The table shows the results for all 95 patients. Among patients who completed the crossover there were no significant differences in vomiting,

receiving cytotoxic regimens without cisplatin we would not advocate routine use of high dose metoclopramide as the cheaper, more easily administered chlorpromazine was equally effective and has less risk of extrapyramidal side effects.

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

	Patients receiving regimens containing cisplatin		Patients receiving regimens not containing cisplatin	
	Metoclopramide (n = 37)	Chlorpromazine (n = 39)	Metoclopramide (n = 48)	Chlorpromazine (n = 45)
Episodes of vomiting:				
None	11 (30)	10 (26)	25 (52)	21 (47)
1-2	10 (27)	6 (15)	18 (37)	7 (16)
3-5	8 (22)	12 (31)	10 (21)	9 (20)
>5	8 (21)	11 (28)	5 (10)	8 (17)
Median No	2	4	1	1
Duration of vomiting (hours):				
None	11 (30)	9 (23)	25 (52)	20 (45)
0-4	10 (27)	7 (18)	8 (17)	6 (13)
4-8	3 (8)	10 (26)	6 (10)	10 (22)
>8	13 (35)	13 (33)	9 (21)	9 (20)
Severity of nausea:				
None	7 (19)	5 (13)	22 (46)	19 (42)
Mild	21 (57)	16 (41)	15 (31)	17 (38)
Moderate	7 (19)	9 (23)	11 (23)	7 (16)
Severe	2 (5)	9 (23)		2 (4)
Duration of nausea (hours):				
None	7 (19)	5 (13)	20 (42)	17 (38)
0-4	8 (23)	5 (13)	8 (17)	9 (20)
4-8	4 (11)	9 (23)	2 (4)	5 (11)
>8	18 (47)	20 (51)	18 (37)	14 (31)
Appetite:				
Improved	2 (5)	2 (5)	4 (8)	2 (4)
Normal	13 (35)	11 (28)	24 (50)	24 (53)
Solids only	10 (30)	10 (26)	10 (21)	9 (20)
Liquids only	12 (30)	16 (41)	10 (21)	10 (23)
Sedation	24 (64)	24 (61)	36 (76)	32 (70)
Diarrhoea	6 (15)	12 (30)	5 (10)	1 (2)
Extrapyramidal reactions	3 (9)		1 (2)	

nausea, or appetite, except that among patients given regimen's containing cisplatin the severity of nausea was significantly less in those who received high dose metoclopramide ($p < 0.01$) and a significant number of these patients preferred high dose metoclopramide (22 v 5, $p < 0.01$); six had no preference. The assessment on the linear analogue scale in this chemotherapy group also favoured high dose metoclopramide ($p < 0.01$). No preference was shown in the group given regimens not containing cisplatin. In both chemotherapy groups there was no significant relation between the order of administration of active drug and drug preference (Fisher's exact test). Adverse effects except extrapyramidal reactions were similar for both antiemetics.

Comment

Analysis of our results showed two clear patterns of control of emesis. In patients receiving cytotoxic regimens containing cisplatin high dose metoclopramide was better than chlorpromazine in controlling nausea. A significant number of patients preferred high dose metoclopramide as an antiemetic and, considering the difficulties in assessing the efficacy of antiemetics, this may be the most valid observation; thus we would recommend use of high dose metoclopramide in cisplatin regimens. In patients receiving cytotoxic regimens without cisplatin, however, both drugs had similar antiemetic efficacy, which suggests that the superiority that high dose metoclopramide has over the phenothiazines in controlling emesis induced by cisplatin¹ may not apply to other cytotoxic drugs. These findings are consistent with the postulate,⁴ based on experimental animal work,⁵ that high dose metoclopramide is particularly effective against emesis due to cisplatin because induction of this is mediated by disorganisation of gastric motility, which is reversed by metoclopramide. Therefore, for patients

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Department of Medical Oncology, Royal Infirmary, Glasgow G4 0SF

DAVID CUNNINGHAM, MB, MRCP, medical registrar
MICHAEL SOUKOP, MB, MRCP, consultant physician
NIGEL L GILCHRIST, FRACP, senior registrar
GORDON J FORREST, MB, senior house officer
ANDREW HEPPELSTONE, MRCP, MRCPATH, Cancer Research Campaign research fellow
IAN T CALDER, MSC, MPS, staff pharmacist

Department of Surgery, Royal Infirmary, Glasgow

COLIN S MCARDLE, MD, FRCS, consultant

Department of Medical Oncology, Woodend Hospital, Aberdeen

ANDREW W HUTCHEON, MD, FRCP, consultant physician

Department of Clinical Oncology, University of Glasgow

STANLEY B KAYE, MD, MRCP, senior lecturer

Correspondence to: Dr D Cunningham.