SHORT REPORTS

Domperidone or metoclopramide in preventing chemotherapeutically induced nausea and vomiting

Severe and sometimes intractable nausea and vomiting are common side effects of cytotoxic chemotherapy. Most doctors prescribe an antiemetic to accompany cytotoxic chemotherapy, but little data exist on which is the most suitable agent.¹ Metoclopramide is a widely used antiemetic, but its side effects include drowsiness, extrapyramidal effects such as dystonia or oculogyric crisis, and convulsions; these are particularly common when the recommended dose is exceeded in children.² Domperidone is a new antiemetic³ that hardly penetrates the blood-brain barrier, and even at doses much greater than therapeutic ones no psychotropic or neurological effects have been observed.⁴ We decided to compare, using a cross-over design, the efficacy of these two antiemetics in preventing nausea and vomiting induced by cytotoxic chemotherapy.

Patients, methods, and results

We used 18 children (6 boys, 12 girls) aged 2-13 years who were selected from the paediatric oncology unit and who were receiving cyclical cytotoxic chemotherapy, which was complicated by nausea and vomiting, for a variety of malignant diseases.

Either intravenous metoclopramide (0.5 mg/kg body weight) or domperidone (up to 1 mg/kg body weight) was given in a random, cross-over design, on at least two occasions immediately before cytotoxic treatment. We did not consider it ethical to include a placebo group. Patients and parents were told that one of two drugs, both effective in controlling vomiting, would be given. Parents or nurses not participating in giving the drugs recorded prodromal symptoms, such as insomnia, anxiety, and vomiting in the 12 hours before treatment, and episodes of nausea and vomiting for a period of 36 hours after treatment.

The incidence of nausea and vomiting on the 20 occasions on which the 18 patients were treated with metoclopramide and domperidone is shown in the table. Prodromal symptoms were similar in both groups. Thirteen

Incidence of nausea and vomiting in 18 children who together received 20 cycles of cytotoxic chemotherapy after prophylaxis with metoclopramide or domperidone

	Metoclopramide	Domperidone
Median No of incidents of nausea	4.5	1.0
Median No of incidents of vomiting	4.0	0.5
No of treatment cycles with more than one incident of nausea	16	12
No of treatment cycles with more than one incident of vomiting	17	10

patients vomited less after domperidone, two vomited more, and three as often as after metoclopramide. Vomiting was significantly reduced after domperidone ($P < 0.01$, McNemar test, two-tailed probability). Domperidone had a considerable effect in the first four hours after cytotoxic treatment, but little protective effect after that, suggesting that its duration of action is about four hours.

Thirteen patients had less nausea after domperidone, one had more, and four were as nauseated as after metoclopramide: a significant difference ($P < 0.01$, McNemar test, two-tailed probability). Patients were followed up at three-weekly intervals, and none experienced any acute symptom that could be implicated as an unwanted effect of either domperidone or metoclopramide. No patient during the study had an unusual fluctuation in blood count or clinical evidence of jaundice, and no patient died.

Comment

Although other studies have shown few neurological side effects associated with domperidone, we decided to use a dose of domperidone that was less than the recommended maximum dose of 1 mg/kg body weight. The patients' subjective response to domperidone was favourable; no patient refused a second treatment, and six patients remarked spontaneously on the benefit gained from domperidone treatment. We think that domperidone offers considerable antiemetic

benefit to children receiving cytotoxic chemotherapy, and that further studies of this type are justified.

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³ Balyens, R, *et al*, *Postgraduate Medical Journal*, 1979, **55**, suppl No 1, p 19.

⁴ Deberdt, R, *Postgraduate Medical Journal*, 1979, **55**, suppl No 1, p 48.

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Clindamycin-associated colonic vasculitis

Pseudomembranous colitis occurring in association with the use of the antibiotic clindamycin has been well documented. We report here what we believe to be the first record of selective colonic vasculitis developing after exposure to this drug.

Case report

A 27-year-old man presented with colicky lower abdominal pain, melaena, and bleeding per rectum. Diarrhoea was not present. He had a 10-year history of sarcoidosis, diagnosed radiologically and confirmed by lymph-node biopsy. He had had recurrent episodes of steroid-responsive hypercalcaemia and on admission was taking prednisolone 10 mg daily. Ten days before he had developed a respiratory infection, which was treated by his family doctor with clindamycin 150 mg four times daily for five days. Examination disclosed mild diffuse lower abdominal tenderness and cervical lymphadenopathy unchanged from that noted before. Haemoglobin concentration was 17.6 g/dl, packed cell volume 0.53 (53%), white cell count $11.7 \times 10^9/l$ (11 700/mm³; neutrophils 71%, lymphocytes 15%, monocytes 13%, eosinophils 1%), and erythrocyte sedimentation rate 39 mm in first hour (Westergren). Biochemical profile and results of urine analysis were normal. Chest x-ray appearances were unchanged from those seen on other occasions but a plain abdominal radiograph showed slight dilatation of the stomach and proximal small bowel. Within 36 hours of admission severe, diffuse, sudden abdominal pain developed. Rectal bleeding was accompanied by fever (38.3°C), tachycardia, and a fall in blood pressure. The abdomen was rigid and bowel sounds were absent. The white cell count was $13.4 \times 10^9/l$ with an unaltered differential. A total colectomy was performed for apparent fulminant colitis. Recovery was complicated by a psychotic state resulting from increased steroid cover. The psychosis resolved with reduced dosage.

The colon showed extensive thickening of the wall. Haemorrhagic areas were present throughout the mucosa, ranging in appearance from solitary, polypoid protuberances up to 2.5 cm diameter to confluent raised zones many centimetres long, which had a coarse, cobblestone appearance. There were no perforations. Microscopy of the affected areas showed widespread acute necrotising vasculitis affecting chiefly the small veins in all layers of the bowel wall. Arterioles were not affected. The submucosal connective tissue was oedematous and haemorrhagic and in severely affected areas there was full-thickness ischaemic necrosis of the mucosa.

Comment

Pseudomembranous enterocolitis related to the use of clindamycin is well recognised and the sigmoidoscopic and pathological features have been clearly defined.¹ Overgrowth of *Clostridium difficile* and the deleterious effect of its toxin on the bowel mucosa may be a causal mechanism in the development of antibiotic-induced enterocolitis,² which is supported by the observation that eradication of the organism with vancomycin often results in resolution of the condition.^{3 4} The

mode of action of the clostridial toxin is not yet clear but it may elicit a local Schwartzman reaction, usually resulting in mucosal changes identical with those of acute ischaemia.^{4,5} In our patient the location of the vascular damage differed from that postulated in classical drug-associated pseudomembranous enterocolitis because the small vessels of the entire bowel wall were affected. Whether this was due to the specific pharmacokinetics of clindamycin or modification of the vascular reaction to putative bacterial toxin by steroids or immunological dysfunction associated with sarcoid, or both, remains speculative.

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Reversal of narcotic-induced delay in gastric emptying and paracetamol absorption by naloxone

Narcotic analgesics inhibit gastric emptying and consequently delay the absorption of orally administered drugs such as paracetamol.¹⁻³ This increases the risk of aspiration of gastric contents during induction of anaesthesia in women in labour after narcotic analgesics and is not reversed by metoclopramide.¹ We have investigated the effect of the specific narcotic antagonist naloxone on narcotic-induced delay in gastric emptying.

Subjects, methods, and results

Gastric emptying and paracetamol absorption (20 mg/kg) were measured simultaneously in four fasting healthy volunteers aged 26-39 years, as described.² Each subject was studied "blind" on three occasions in random order at least seven days apart, once after placebo injections, once 30 minutes after pentazocine 60 mg intramuscularly, and once 30 minutes after pentazocine and immediately after naloxone 1.2 mg intravenously.

Gastric emptying and paracetamol absorption were rapid in all the control studies (see table). The mean time to empty half of the ingested dose was 13 minutes and the mean peak plasma paracetamol concentration 23.8 mg/l 22.5 minutes after ingestion. After pentazocine, however, gastric emptying and paracetamol absorption were greatly delayed in all subjects. Fifty per cent gastric emptying occurred at 97.3 minutes ($P < 0.02$; paired t test). The mean peak plasma paracetamol concentration was only 10.8 mg/l, which occurred 160 minutes after ingestion ($P < 0.05$ and $P < 0.01$ respectively). This inhibition was largely reversed by naloxone. The gastric-emptying measurements and mean time to peak plasma paracetamol concentration after pentazocine and naloxone did not differ significantly from control values (27.8 minutes and 25 minutes respectively). Nevertheless, the mean peak paracetamol concentration was only 15.0 mg/l, which was significantly lower than control values ($P < 0.05$). This may reflect the short duration of action of naloxone compared with pentazocine. The total amount of paracetamol absorbed was not influenced by pentazocine administered alone or with naloxone. In the control studies 75%, 79%, and 74% of the

administered doses of pentazocine and pentazocine and naloxone were recorded in the urine over 24 hours.

Comment

Gastric emptying and paracetamol absorption are severely inhibited by narcotic analgesics, and the delay in gastric emptying observed in women during labour is almost certainly attributable to narcotic analgesics. Metoclopramide does not reverse this delay.¹ In this study naloxone largely reversed the effect of pentazocine on gastric emptying, though its effect was probably shorter. Larger doses of naloxone may produce a greater reversal of pentazocine's effects, and naloxone may more effectively reverse the effects of a pure narcotic agonist such as pethidine. When reversal of the effects of narcotic analgesics on gastric emptying is desirable—for example, immediately before anaesthesia during labour or in recurrent vomiting—intravenous naloxone reverses the delay in gastric emptying as well as the other effects of narcotics.

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Isolation of *Legionella pneumophila* from blood culture

The severe lobar type of pneumonia and the other manifestations of legionnaires' disease^{1,2} all support occurrence of an early bacteraemic phase in the illness. Though the causative organism has been cultured from lung tissue, pleural exudate, bronchial aspirate, and sputum on bacteriological media,^{3,4} it has proved difficult to demonstrate in blood.⁵ In the case now reported *Legionella pneumophila*, serogroup 1, was recovered in broth culture from blood before death and also from postmortem lung tissue by inoculation on bacteriological medium and into yolk sacs of fertile hens' eggs.

Case report

A retired 61-year-old man who had worked as a factory cleaner was admitted to hospital in a semi-conscious state. He was a heavy smoker with a history of chronic cough and extreme breathlessness on exertion. A partial gastrectomy two years previously because of haematemesis from a peptic ulcer had been followed then by an episode of left ventricular failure, from which he had recovered. More recently he had been reasonably well until a week before admission, when his cough exacerbated with production of brownish sputum. His condition deteriorated slowly and after five days amoxycillin was started. Despite this treatment, increasing dyspnoea and drowsiness led to emergency admission. Urgent chest radiography showed extensive opacity on the left side. His haemoglobin concentration was 15.5 g/dl and white cell count $6 \times 10^9/l$ ($6000/mm^3$) with 85% neutrophils. Blood was taken for culture and treatment for his chest infection and heart condition started. He suffered respiratory and cardiac arrest, however, and died five hours later.

Blood was cultured in enrichment-broth medium of the following composition: Difco (yeast extract 5 g, proteose peptone 15 g); panmede liver extract 2.5 g; L-cysteine HCl H_2O 0.4 g; ferric pyrophosphate soluble 0.125 g; sodium chloride 5 g; deionised water 1 l. After dissolving the ingredients the pH was adjusted to 6.9 and the medium sterilised by autoclaving at 121°C for 15 minutes. *Legionella pneumophila* were observed in the culture after five days' incubation, identified first with Gram's stain, dilute carbol fuchsin being the counter-stain, and confirmed as serogroup 1 by direct fluorescent antibody test followed by subculture on solid medium.⁴ Lung tissue in a 10% suspension was inoculated directly on enriched blood agar medium⁶ and incubated at 36°C in a humid atmosphere containing 5% CO_2 . Typical colonies of *L. pneumophila* were detectable after three days' incubation and were identified as serogroup 1 in similar fashion to the blood culture.

Effect of pentazocine and pentazocine/naloxone on gastric emptying and paracetamol absorption

	Mean ($\pm$ SE) time to 50% gastric emptying (minutes)	Mean ($\pm$ SE) peak plasma paracetamol concentration (μ g/ml)	Mean ($\pm$ SE) time to peak concentration (minutes)
Control	13.0 $\pm$ 3.5	23.8 $\pm$ 1.9	22.5 $\pm$ 1.3
Pentazocine .. .	97.3 $\pm$ 17.6	10.8 $\pm$ 0.6	160.0 $\pm$ 16.3
Pentazocine/naloxone ..	27.8 $\pm$ 7.6	15.0 $\pm$ 1.8	25.0 $\pm$ 1.8