The meaning of the slow radiological healing of fractures or Looser zones in three of the seven patients in whom they were present is uncertain, as partially mineralised osteoid, which is radio-opaque, may appear around the fractures without there being any true remodelling and healing of trabecular bone. There was no improvement in histological osteomalacia in these cases.

Histologically, osteomalacia became worse in eight patients, three of whom showed an appreciable increase in osteitis fibrosa, and improved in only one. There is thus no evidence that phosphate treatment—or induction of osteitis fibrosa—promotes healing of osteomalacia.

The effect of phosphate treatment on myopathy and on bone pain, which was present in those with severe myopathy, is more difficult to assess. Assessment of myopathy is affected by the patient's motivation, which may have a large role in patients selected for special treatment. Nevertheless, two patients showed unequivocal improvement of myopathy, though not of bone histology; one was wheelchair-bound at the start of therapy through weakness and pain, was walking within three months, and is now clinically normal. The cause of these changes may be questioned, however, as 1α -OHD₃, which she started at the same time as phosphate treatment, may sometimes help myopathy in renal osteodystrophy,¹⁸ and she has indeed continued to improve since stopping phosphate treatment. But the other patient who improved appreciably had been taking 1α -OHD₃ for two years without improvement before starting phosphate. Four patients became progressively weaker and suffered increasing pain during the course of treatment. Review of all 30 patients we have treated shows similar results; of 22 who had initial symptoms, two showed appreciable improvement, six subjective improvement, one an apparent transient improvement, and six no change; while four could not be assessed and five deteriorated. We could not predict which patients were the potential responders from the initial clinical, biochemical, radiological, or histological findings, or from changes during treatment.

The most frequent clinical complications of phosphate treatment—pruritus and stiffness of joints and muscles—could be controlled by reducing the dose in all except two patients, who stopped treatment after two months. There is a great theoretical risk of inducing ectopic calcification in a group of patients with high serum phosphate concentrations whose calcium concentration level is maintained with vitamin D derivatives. The incidence or importance of this cannot easily be assessed

over a six-to-12-month period, especially as many patients already had corneal or arterial calcification at the start of the trial. Nevertheless, three of the 30 patients showed a definite increase in arterial calcification, and three new corneal calcification.

Our patients on dialysis with osteomalacia have similar serum phosphate concentrations to those without osteomalacia. Phosphate depletion without hypophosphataemia has not been recorded as causing osteomalacia in other circumstances. Our results suggest similarly that in patients on dialysis who are not hypophosphataemic phosphate depletion is not a cause of osteomalacia. Our policy now is to use phosphate therapy only in patients with persistent predialysis or severe postdialysis hypophosphataemia.

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SIDE EFFECTS OF DRUGS

Erosive gastritis and duodenitis during continuous cimetidine treatment

Cimetidine accelerates the healing of duodenal ulcers, and symptomatic improvement is usually accompanied by endoscopic evidence of healing.^{1 2} We report an unusual mucosal appearance that developed in a patient receiving continuous cimetidine treatment.

Case report

A 43-year-old man presented with a typical history of peptic-ulcer disease of 14 years' duration. Barium-meal examination in January 1976 showed a shallow ulcer 5 mm in diameter on the anterior wall of the duodenal bulb with associated duodenal scarring and deformity. The gastric mucosa was normal apart from a mild antral gastritis. The patient agreed to participate in a six-month pharmacokinetic study of cimetidine, and treatment was started at 800 mg/day. Compliance with treatment was checked by tablet counts at monthly intervals. Symptomatic relief was complete within a few days and

continued throughout the study period, during which no other drugs were given.

Three months after starting treatment repeat endoscopy showed complete healing of the ulcer. Widespread punctate erosive gastritis was noted, however, with altered blood at some erosion sites; there was also a florid duodenitis, with several areas of punctate erosion. Three months later endoscopy showed an almost identical appearance. On each occasion the patient had no symptoms and said that he had taken neither aspirin nor alcohol. Blood urea and electrolyte concentrations, liver function values, and routine haematological tests assessed at monthly intervals remained normal throughout. At six months a blood sample taken six hours before endoscopy showed no trace of either salicylate or alcohol. Four months after stopping treatment the patient was still asymptomatic and endoscopy showed no evidence of erosive gastritis, although duodenitis was still present. A pentagastrin test showed a basal acid output of 10.8 mmol(mEq)/h and a stimulated acid output of 58.9 mmol(mEq)/h.

Comment

These endoscopy appearances usually occur in patients who have recently taken either aspirin or alcohol or both. We were satisfied that our patient had taken neither. During our study over 40 endoscopic examinations were carried out on patients receiving continuous

cimetidine treatment, and this appearance was not seen in any other case. We are not aware of any similar report.

The meaning of our findings is not clear. Cimetidine may arrest bleeding from gastric erosions³ but has not been shown to heal such lesions, and their natural history is still not understood. It is therefore of great interest, if this agent really is responsible for stopping bleeding from gastric erosions, that bleeding erosive gastritis should occur during continuous cimetidine treatment.

¹ Bodemar, G, and Walan, A, *Lancet*, 1976, 1, 161.

² Gillespie, G, et al, in *Proceedings of 2nd International Symposium on Histamine H₂ Receptor Antagonists*, ed W L Burland and M A Simkins, p 240. Amsterdam, Excerpta Medica, 1977.

³ MacDougall, B R D, Bailey, R J, and Williams, R, in *Proceedings of 2nd International Symposium on Histamine H₂ Receptor Antagonists*, ed W L Burland and M A Simkins, p 329. Amsterdam, Excerpta Medica, 1977.

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Department of Therapeutics and Clinical Pharmacology, University of Aberdeen, Aberdeen AB9 2ZD

J WEBSTER, MB, MRCP, lecturer
J C PETRIE, MB, MRCP, senior lecturer

Gastrointestinal Unit, Woodend General Hospital, Aberdeen AB9 2YS

N A G MOWAT, MB, MRCP, consultant physician

Raised intracranial pressure due to perhexiline maleate

Although perhexiline maleate is valuable in treating angina, its side effects are becoming more widely recognised and have recently been the subject of an "adverse reactions" letter from the Committee on Safety of Medicines.¹ Neurological complications are prominent among adverse effects of perhexiline, and we report three cases of raised intracranial pressure.

Case reports

Case 1—A 51-year-old man first developed angina pectoris in 1973. This was treated with practolol and glyceryl trinitrate. Propranolol was later substituted for the practolol. He had been treated for depression for several years with amitriptyline. His chest pains were well controlled until June 1976, when perhexiline maleate 100 mg twice a day was introduced. This was increased to 200 mg twice a day in August 1976 with good effect. He presented with severe headaches and unsteadiness in April 1977. Examination showed gross bilateral papilloedema with fundal haemorrhages, ataxia of gait, and dysidiadochokinesia. No other focal neurological abnormality was found, and there was no evidence of a peripheral neuropathy. The blood pressure was normal and the visual acuity was unimpaired. An x-ray film of the skull showed nothing abnormal. Computerised axial tomography (CAT scan) showed slightly dilated lateral ventricles, but no evidence of a cerebrospinal fluid (CSF) block. There was no suggestion of a mass lesion. The only change in his treatment was to withdraw perhexiline. Within four weeks the ataxia was better and within six weeks the fundi were normal. Lumbar puncture at this stage showed the CSF pressure to be 130 mm Hg and the protein content 1.0 g/l. He had been on perhexiline for 11 months, at a dose of 400 mg/day for nine months.

Case 2—A 43-year-old woman first developed angina pectoris in 1971. Coronary angiography showed normal coronary arteries, and she was

subsequently treated with various beta-blockers and glyceryl trinitrate. Chest pains increased so perhexiline maleate 100 mg three times a day was introduced in April 1976 with good effect. She presented in April 1977 with a one-month history of unsteadiness, headache, and nausea. Examination showed bilateral papilloedema with haemorrhages. Apart from a slight ataxia, there were no other focal neurological signs, and no evidence of peripheral neuropathy. The blood pressure was normal. Liver function was abnormal—serum alanine aminotransferase 163 IU/l (normal <30 IU/l), serum alkaline phosphatase 329 IU/l (normal <275 IU/l). The skull x-ray film and isotope brain scan showed nothing abnormal. CAT scan showed normal-sized ventricles and no evidence of a mass lesion. The CSF was not examined. The only change in her treatment was to withdraw perhexiline. Her symptoms of headaches and unsteadiness disappeared in four weeks, and the fundal appearances improved greatly. Nevertheless, four months after stopping the drug, the fundal appearances were still not quite normal. Visual acuity remained unimpaired. Liver function also returned to normal. She had been taking perhexiline 300 mg/day for 12 months.

Case 3—A 40-year-old woman developed angina pectoris in 1974. Coronary angiography showed normal coronary arteries. Later that year she had a small myocardial infarction, after which her angina became worse. This was not adequately controlled by propranolol, and treatment with perhexiline twice daily was started in July 1975. She was entered into a clinical trial of perhexiline, and her angina improved. In November 1975 she suffered a pulmonary embolus and was anticoagulated with warfarin. In April 1976 she presented with a six-week history of headaches and unsteadiness; she also described numbness and weakness of her arms and legs. Examination showed bilateral papilloedema and ataxia of gait. There was no clinical suggestion of a peripheral neuropathy, but nerve-conduction studies were not done. Skull x-ray film, isotope brain scan, ventriculography, and CAT scan showed nothing abnormal. Perhexiline was stopped, and the fundal appearances gradually improved. Her ataxia and sensory symptoms disappeared. But 11 months after stopping the drug the optic discs were still not quite normal. Visual acuity was impaired at presentation (6/24 right eye, 6/9 left eye), and this did not improve. She had been on perhexiline 200 mg/day for 10 months.

Comment

Papilloedema has been seen before in patients taking perhexiline. Of seven patients considered to have peripheral neuropathy induced by perhexiline, three also had papilloedema.² These patients had been taking 300–400 mg/day for more than a year, and the papilloedema improved within six weeks of stopping the drug. In one patient the fundal appearances were seen to return completely to normal. Each of our three patients had been on perhexiline for at least 10 months, and the improvement in the fundal appearances coincided with stopping the drug, only the third patient showing a permanent impairment of visual acuity. Prolonged medication has been a feature in many cases of neuropathy³ and myopathy.⁴ Clearly, ataxia and headaches also occur fairly often as side effects of perhexiline without evidence of raised intracranial pressure.⁵

¹ Committee on Safety of Medicines, *Adverse Reactions Series*, No 15, July 1977.

² Bousser, M G, et al, *Coeur et Médecine Interne*, 1976, 15, 181.

³ Lhermitte, F, et al, *British Medical Journal*, 1976, 1, 1256.

⁴ Tomlinson, I W, and Rosenthal, F D, *British Medical Journal*, 1977, 1, 1319.

⁵ *Drug and Therapeutics Bulletin*, 1976, 14, 97.

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Good Hope General Hospital, Sutton Coldfield, West Midlands B75 7RR

W P STEPHENS, MB, MRCP, medical registrar
J D EDDY, MB, MRCP, consultant physician

Dudley Road Hospital, Birmingham B18 7QH

L M PARSONS, MB, MRCP, registrar in neurology
S P SINGH, MB, FRCP, consultant cardiologist