SHORT REPORTS

Cimetidine interaction with phenytoin

Cimetidine inhibits the hepatic microsomal oxidation system *in vitro* and reduces clearance of drugs metabolised by these enzymes.¹ In man cimetidine increases the effect of warfarin^{2,3} and diazepam.⁴

Phenytoin, a commonly used anticonvulsant with a narrow therapeutic index, is also metabolised by the hepatic microsomal system. We therefore investigated the effect of cimetidine on steady-state plasma phenytoin concentrations in patients with longstanding epilepsy.

in free urinary phenytoin would be consistent with this. Alternatively, but less likely, cimetidine may have caused an increase in phenytoin bioavailability.

Cimetidine and phenytoin are often prescribed, and concurrent administration will therefore occur in some patients. Our findings show that caution is necessary when adding cimetidine to phenytoin treatment, especially when plasma concentrations are already in the upper therapeutic range.

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Patients studied and mean serum phenytoin concentrations ($\pm$ SD) before, during, and after cimetidine (C)

Case No	Age (years)	Phenytoin dose (mg/day)	Other drugs	Mean plasma phenytoin (μ mol/l)*		
				Before C	During C	After C
1	27	400	Carbamazepine	74.7 $\pm$ 5.8	99.2 $\pm$ 6.3†	89.4 $\pm$ 11.0
2	20	260	Valproate, primidone	63.8 $\pm$ 3.1	82.6 $\pm$ 6.7†	74.5 $\pm$ 2.1
3	33	300	Clonazepam, primidone	45.4 $\pm$ 3.9	52.7 $\pm$ 4.5†	48.0 $\pm$ 0.7
4	63	300	Phenobarbitone	33.8 $\pm$ 3.8	40.3 $\pm$ 3.5†	36.0 $\pm$ 0.0

*Therapeutic range 40–80 μ mol/l (10–20 μ g/ml).

†p < 0.02 compared with value before cimetidine.

Conversion: SI to traditional units—Phenytoin: 1 μ mol/l $\approx$ 0.25 μ g/ml.

Patients, methods, and results

Plasma phenytoin concentrations were measured in four epileptic volunteers (table) by EMIT (Syva, Palo Alto, California) on three to five separate days in the week before cimetidine administration, on five or six days during cimetidine administration, and up to six days afterwards. Blood samples were taken at 7 am, before breakfast, in the three inpatients and at 4.30 pm each day in the single outpatient (case 4). Cimetidine 200 mg thrice daily with meals and 400 mg at night was given for six days. Dosage of all other drugs was unchanged for the two weeks before and during the study. A 24-hour urine collection in each patient was obtained before and during cimetidine administration for measurement of free phenytoin and its main metabolite, 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (*p*-HPPH). Urinary free phenytoin and total *p*-HPPH were measured by gas chromatography and mass spectrometry after preparation by the method of Sawchuk and Cartier.⁵ Liver function values were normal in all patients. Renal function was normal in all except one patient (case 4), who had a steady serum creatinine concentration of 190 μ mol/l (2.1 mg/100 ml; normal range 50–120 μ mol/l (0.6–1.4 mg/100 ml)). The unpaired *t* statistic was used to analyse changes in serum phenytoin concentrations for individual patients, and the paired *t* statistic to compare urinary excretion of phenytoin and *p*-HPPH, before and during cimetidine treatment.

Cimetidine produced a significant increase in the plasma phenytoin concentration in each patient (table). Mean 24-hour urinary outputs of *p*-HPPH and phenytoin increased from 122.5 to 201.5 mg and from 6.8 to 12.0 mg respectively. One patient (case 1) developed symptoms consistent with mild phenytoin intoxication during cimetidine administration, which disappeared when cimetidine was stopped. When cimetidine was withdrawn plasma concentrations of phenytoin tended to fall towards values found before cimetidine administration (table).

Comment

The addition of a standard dose of cimetidine was associated with a 13–33% increase in mean plasma phenytoin values. This effect was clinically important in one patient (case 1), who became mildly clinically intoxicated. A rise in plasma phenytoin concentration was seen in all patients within 48 hours of beginning cimetidine. Two patients (cases 3 and 4) appeared to achieve a new steady state of plasma phenytoin concentration after five days of cimetidine. A clear plateau was not obtained by the time of cimetidine withdrawal in two patients (cases 1 and 2) whose plasma phenytoin concentrations were in the higher range associated with changing elimination kinetics. In these patients continued cimetidine administration might have resulted in even higher phenytoin values.

Our results do not explain the mechanism of the interaction. An unexpected rise in urinary *p*-HPPH concentration occurred in each patient and makes it unlikely that cimetidine inhibited metabolism of phenytoin to *p*-HPPH. Possibly cimetidine blocked one of the other metabolic pathways responsible for phenytoin degradation. The rise

¹ Puurunen I, Pelkonen O. Cimetidine inhibits microsomal drug metabolism in the rat. *Eur J Pharmacol* 1979;55:335–6.

² Serlin MJ, Sibeon RG, Mossman S, *et al*. Cimetidine: interaction with oral anticoagulants in man. *Lancet* 1979;ii:317–9.

³ Hetzel D, Birkett D, Miners J. Cimetidine interaction with warfarin. *Lancet* 1979;ii:639.

⁴ Klotz U, Anttila VJ, Reimann I. Cimetidine/diazepam interaction. *Lancet* 1979;ii:699.

⁵ Sawchuk RJ, Cartier LL. Liquid-chromatographic method for simultaneous determination of phenytoin and 5(4-hydroxyphenyl)-5-phenylhydantoin in plasma and urine. *Clin Chem* 1980;26:835–9.

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Late benign intrathoracic gastric perforation after oesophagectomy for carcinoma

Late benign perforation of the intrathoracic stomach after oesophagectomy and anastomosis is apparently extremely rare. We describe such an event occurring 13 years after oesophagectomy for a squamous-cell carcinoma of the lower third of the oesophagus.

Case report

A 50-year-old man presented in January 1962 with worsening dysphagia. A sliding hiatus hernia had been found in 1947. Barium-swallow examination, oesophagoscopy, and biopsy showed a squamous-cell carcinoma in the lower third of the oesophagus. An Ivor Lewis type of resection was performed in February 1962. The stomach was mobilised, leaving the right gastric and gastroepiploic arteries. After a pyloromyotomy the gastric remnant was closed with chromic catgut in layers. The anastomosis was placed into the anterior aspect of the stomach using silk sutures. Histological examination of

the resected specimen confirmed a squamous-cell carcinoma, with metastases in one of three mediastinal lymph nodes. Radiotherapy was not given.

He remained well until February 1972, when he developed acute bronchitis. At that time minor symptoms of oesophageal reflux were noted and barium-swallow examination showed no recurrence or any delay in gastric emptying or screening. His bronchitis persisted with the development of asthma, necessitating admission and treatment with corticosteroids in October 1975. Two months later, while still receiving steroid treatment, he was admitted as an emergency with an intrathoracic perforation of the gastric remnant (figure (a)). After intrathoracic drainage and resuscitation right thoracotomy showed two benign peptic ulcers on the anterior wall of the stomach, away from the oesophagogastric anastomosis. Both ulcers had perforated. They were excised and the stomach closed. No recurrent tumour was seen.

Chest radiographs (a) at time of gastric perforation; (b) after recovery and discharge from hospital.

The patient recovered and returned to work with a small sinus persisting in the centre of the wound (figure (b)). In August 1976 the sinus discharge increased and he was admitted for further investigations and exploration of the wound. Before surgery was undertaken, however, he developed sudden left hemiplegia and died shortly afterwards. Postmortem examination was not performed.

Comment

Survival after oesophagectomy for carcinoma is rare beyond 10 years¹; two patients have been reported alive at 13² and 31 years.³ Perforation in the gastric remnant may be benign; and this usually occurs within a year, often after radiotherapy. Radionecrosis of the stomach wall is implicated as a cause. Perforation of the oesophagogastric anastomosis has occurred into the heart one year after surgery.⁴ Recently it has been shown that if the blood supply to the mobilised stomach depends on the right gastroepiploic artery the lesser curve is relatively ischaemic.⁵

Anastomotic leakage is a complication with a high mortality rate.¹ Gastric stasis predisposes both to leakage and to benign perforation, and the importance of a drainage procedure is accepted. Other factors associated with ulcer formation in the intrathoracic gastric remnant include the use of non-absorbable sutures, injury after instrumentation, and ingestion of drugs. In our patient we can discount stasis, ischaemia, and radionecrosis. He had non-absorbable sutures at the oesophagogastric anastomosis, but the perforations were not in the suture line. He had not been subjected to any instrumentation. Probably the corticosteroids contributed to the perforation of the

ulcers, since this event occurred within the relatively short period of eight weeks from the start of treatment.

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- ¹ Gunnlaugsson GH, Wychulis AR, Roland C, Ellis FH. Analysis of the records of 1,657 patients with carcinoma of the oesophagus and cardia of the stomach. *Surg Gynecol Obstet* 1970;**130**:997-1004.
- ² Torek F. Survival for thirteen years after oesophagectomy for carcinoma. *JAMA* 1913;**60**:1533.
- ³ Franklin RH. Long-term survival after resection of carcinoma of the oesophagus. *Br Med J* 1978;iii:1268-9.
- ⁴ Prolla JC, Taebel DW, Kirsner JB. Perforation of an oesophagogastric anastomotic ulcer into the left atrium. Case report and review of the literature. *Gastroenterology* 1967;**52**:871-4.
- ⁵ Thomas DM, Laingford RM, Russell RCG, Le Quesne LP. The anatomical basis for gastric mobilisation in total oesophagectomy. *Br J Surg* 1979;**66**:230-3.

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Diphtheroid endocarditis after electrolysis

Diphtheroid bacilli are an uncommon, albeit recognised, cause of endocarditis, most often affecting prosthetic heart valves.¹ Lipophilic diphtheroids form a large, incompletely classified group of bacteria commonly isolated from normal skin.² We describe a young woman who developed diphtheroid endocarditis during treatment with electrolysis for facial hair. We believe this to be a unique portal of endocardial infection by an organism that is rarely responsible for endocarditis.

Case report

A 19-year-old Greek girl had had rheumatic fever when aged 11 years. At age 17 she had been admitted to a major teaching hospital for orthodontic surgery. Although she had been asymptomatic, moderate aortic incompetence had been detected on clinical examination and the diagnosis supported by echocardiography. Some three months before her illness she had started a course of electrolysis for facial hair. She had continued twice-weekly treatments until a week after the onset of the first symptoms—and then presented to her general practitioner with a two-and-a-half-week history of night sweats, rigors, increasing lethargy, and dyspnoea of effort. She also had a rash over her legs.

Her general practitioner took three sets of blood cultures over a three-day period, all of which grew the same Gram-positive bacillus. This was eventually classified as a lipophilic group I bacillus by its lipid growth requirements and sugar fermentation, according to the classification of Smith.² Because these cultures were initially reported as skin contaminants she was not admitted to hospital until the third day after presentation. The same organism was recovered from a fourth blood culture taken at the time of admission. When she was examined on admission the temperature was 38.7°C. A sparse macular rash was noted over the legs. Blood pressure was 130/40 mm Hg and pulse rate 108 beats/min. There were peripheral and auscultatory findings of moderate aortic incompetence. A triple rhythm and an Austin-Flint murmur were also present. Haemoglobin concentration was 15 g/dl and white cell count $7.9 \times 10^9/l$ ($7900/mm^3$) with 59% polymorphs, 30% lymphocytes, 8% monocytes, and 3% eosinophils. Toxic granulation was present. The erythrocyte sedimentation rate was 61 mm in the first hour. Cryoglobulins were not detected. Examination of a mid-stream urine specimen showed no abnormality.

She was started on intravenous benzylpenicillin, 4 million units four hourly, oral probenecid 500 mg twice daily, and intramuscular streptomycin 0.5 twice daily. In-vitro sensitivity testing showed the organism to be sensitive to penicillin, tetracycline, and lincomycin. It was resistant to streptomycin, and synergism to streptomycin and penicillin was not shown. A trough penicillin concentration was 19 µg/ml and, as the organism was