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