empirically to give the "best fit" when compared with subjective assessment of noise annoyance.[8-10]

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# Cimetidine for duodenal ulceration in patients undergoing haemodialysis

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## Summary

**Peptic ulcer is a common problem in advanced renal failure, but most drugs for ulcers are hazardous in this condition. In a small open study cimetidine was given to nine patients with acid hypersecretion and endoscopically diagnosed duodenal ulceration who were undergoing haemodialysis. The patients obtained good pain relief and suffered no serious side effects. Both basal and stimulated acid output fell considerably and the plasma gastrin response to food increased during treatment. Two patients with recurrent vomiting during haemodialysis had a striking response to cimetidine, which suggested that such vomiting may be acid-mediated in some patients.**

**These preliminary results suggest that cimetidine may prove to be an advance in the management of peptic ulcer in uraemic patients.**


## Introduction

Peptic ulceration is unusually common in chronic renal failure,[1] and this poses a difficult problem, since many drugs for ulcer may have undesirable side effects in the uraemic patient. The $H_2$-receptor antagonist cimetidine is excreted mainly by the kidneys, but in patients on regular dialysis a reduced dose will produce adequate blood concentrations without the risk of accumulation.[2] Furthermore, an acid-lowering drug is a logical approach in the uraemic patient, as pyloroduodenal ulcer predominates in this condition, and gastric hyperacidity is strongly implicated.[3] We present here our preliminary findings in patients undergoing renal dialysis who suffered peptic ulceration and were treated with cimetidine.


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## Patients and methods

Nine patients were treated with cimetidine. All had end-stage chronic renal failure (creatinine clearances $<3$ ml/min) requiring support by regular haemodialysis, and all had endoscopically proved duodenal or pyloric ulceration with gastric acid hypersecretion (peak acid output $>45$ mmol (mEq)/h for men, $>30$ mmol/h for women; or basal acid output $>5$ mmol/h).

Cimetidine was given for six weeks in a reduced dose of 400 mg/day on non-dialysis days and 800 mg/day on dialysis days, as a single haemodialysis is known completely to clear the drug from the blood. Maintenance treatment of 200 mg/day was continued thereafter.

### ASSESSMENT

The symptomatic response was recorded at the end of six weeks, and repeat endoscopy carried out in those who had an ulcer crater before treatment. (Repeat endoscopy was not carried out in those who initially showed chronic scarring and deformity). All patients had two pentagastrin tests and two standard meal tests to assess, respectively, the effect of treatment on gastric acidity and plasma gastrin response to food. The tests were performed before treatment and again at the mid-point of the initial six-week course. A 200 mg dose of oral cimetidine was given one hour before the repeat test.

Gastric acidity was measured using the standard method of intramuscular pentagastrin stimulation (6 $\mu$g/kg body weight), and plasma gastrin was measured by radioimmunoassay.[4] (Normal values for plasma gastrin in this laboratory are 0–150 ng/l.) The standard meal used consisted of 50 g carbohydrate, 18 g protein, and 20 g fat given as lean cooked ham, white crustless bread, butter, unsweetened orange juice, and a cup of tea with milk. The test was carried out after an overnight fast of 10 hours, and blood samples were withdrawn through an indwelling needle inserted into a forearm vein.

The following haematological and biochemical indices were measured on all patients before and after six weeks' treatment: total and differential white cell count, platelet count, and serum creatinine and transaminase concentrations.

The significances of differences were calculated using the paired $t$ test.

## Results

Clinical details before treatment are given in the table. All but one patient had dyspeptic symptoms of varying degree, and two also had persistent vomiting on days of dialysis. After six weeks' cimetidine treatment all but one patient, who had active ulcer craters, showed almost complete resolution of symptoms, and the two patients with recurrent vomiting showed a quite dramatic response: their vomiting ceased immediately treatment began. The craters in the other three patients with active disease had healed by the end of six weeks. No serious side effects occurred.

When gastric acid was measured after three weeks' treatment both basal and stimulated acid output showed a considerable reduction (of 91% and 57% respectively; fig 1).

The repeat standard meal test showed that the serum gastrin response was increased significantly when the food stimulus was preceded by cimetidine (fig. 2).

No significant change was seen in the haematological or biochemical indices measured before and after treatment.

*Clinical data before cimetidine treatment*

| Case No | Sex | Age (years) | Serum gastrin (pg/ml) | Basal acid output (mmol/h) | Peak acid output (mmol/h) | Endoscopy |
|---|---|---|---|---|---|---|
| 1 | M | 33 | 170 | 2·6 | 47·6 | Chronic duodenal ulcer |
| 2 | M | 15 | 120 | 9·1 | 31·4 | Active duodenal ulcer |
| 3 | F | 40 | 85 | 6·9 | 23·4 | Active duodenal ulcer |
| 4 | M | 40 | 120 | 3·8 | 78·0 | Chronic duodenal ulcer |
| 5 | M | 48 | 220 | 7·8 | 41·2 | Chronic prepyloric ulcer |
| 6 | M | 35 | 235 | 8·9 | 61·6 | Active duodenal ulcer |
| 7 | M | 48 | 130 | 3·7 | 67·0 | Active duodenal ulcer |
| 8 | F | 51 | 205 | 3·7 | 52·4 | Chronic duodenal ulcer |
| 9 | F | 20 | 585 | 9·2 | 38·2 | Chronic duodenal ulcer |

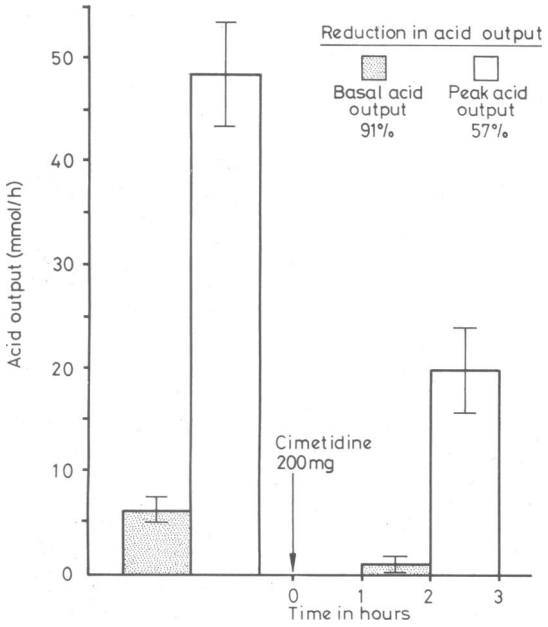


FIG 1—Effect of cimetidine on gastric acid secretion in eight uraemic patients with duodenal ulcer. Results are mean (± SE of mean) basal and peak acid output before and after treatment.

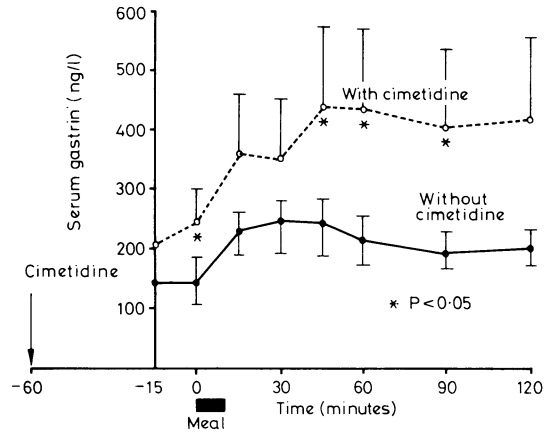


FIG 2—Effect of oral cimetidine on plasma gastrin response to food in eight uraemic patients with duodenal ulcer. Results are means (± SE of mean).

*Conversion: SI to traditional units*—Acid output: 1 mmol/l = 1 mEq/l.

## Discussion

Drugs for peptic ulcer may have serious side effects in the presence of impaired renal function, and most of the commonly used antacids fall into this category. Magnesium trisilicate mixture contains enough sodium to reverse the beneficial effects of the low sodium diets used in renal hypertension[5]; aluminium-containing antacids have recently been implicated in causing dialysis dementia[6]; calcium antacids have been shown actually to stimulate gastric acid secretion after the initial buffering action has occurred[7]; the liquorice derivatives affect sodium and potassium handling by the kidney; and bismuth toxicity may occur with preparations containing colloidal bismuth. Drugs that give symptomatic relief or heal ulcers are therefore potentially dangerous in patients with impaired renal function.

Our preliminary results show that cimetidine, in reduced doses, is well tolerated by patients with end-stage renal failure on maintenance haemodialysis. The acid suppression achieved is impressive in view of the fact that, under the conditions of this study, nasogastric aspiration may have removed some of the ingested dose. Cimetidine has been reported to increase plasma creatinine and serum transaminase concentrations,[8] but we found no evidence of this among our patients.

The two patients with recurrent vomiting during haemodialysis showed a considerable improvement on cimetidine. Both showed abrupt cessation of vomiting followed by weight gain and improvement in general wellbeing. Both these patients had acid hypersecretion with pyloroduodenal scarring and deformity due to chronic ulceration. As basal gastric acidity is known to be increased by haemodialysis,[9] this vomiting may have represented temporary pyloric obstruction due to acid-mediated mucosal oedema or spasm.

It may be suggested that the effect of cimetidine on gastrin release in response to food is undesirable when there is already a degree of gastrin overdrive on the parietal cell, as in the uraemic patient. Whether this will result in acid rebound on stopping treatment remains to be seen. Our overall impression from this preliminary study has, however, been favourable, and the results indicate that cimetidine should be further evaluated in this condition.

After kidney transplantation there is considerable mortality from upper gastrointestinal haemorrhage and perforation.[10] There may therefore be a case for giving a prophylactic antisecretory drug to patients with duodenal ulcer and raised or normal gastric acidity during the high-risk period when corticosteroid dosage is necessarily high—that is, during the first six months after operation[11] and later during rejection episodes. A significant proportion of uraemic patients are, however, hypochlorhydric or achlorhydric,[12] and it is therefore irrational to advocate universal treatment with an acid-lowering drug. It is worth pointing out that ulcers should be sought by endoscopy. The barium meal examination in patients with chronic uraemia often shows a coarsening of mucosal folds,[13] which makes interpretation of the radiological appearances difficult.

We must also emphasise that upper gastrointestinal tract complications after transplantation may be due to acute gastric erosions,[12] and the place of a prophylactic antisecretory agent in preventing these lesions is as yet undecided. Nevertheless, the

incidence and severity of gastric erosions would clearly be minimised if drugs with an erosive influence (corticosteroids) were used sparingly and azathioprine and other cytotoxic drugs that may contribute a bleeding tendency (actinomycin C, cyclophosphamide, antilymphocyte globulin) given in as low a dosage as possible. Patients should also be warned of the danger of aspirin-containing preparations.[14] Fibreoptic endoscopy and measurement of gastric acidity are therefore necessary to identify patients likely to benefit from prophylactic use of an antisecretory drug, and attention to immunosuppressive drug regimens is equally important. This seems preferable to prophylactic surgery, which is the policy in some dialysis centres.[15 16]

In conclusion, cimetidine may prove to be a considerable advance in the management of peptic ulcer in the uraemic patient and also in the prevention of upper gastrointestinal complications after transplantation.

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# Glutamate dehydrogenase: a reliable marker of liver cell necrosis in the alcoholic

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## Summary

**The usefulness of blood enzyme determinations as markers of liver necrosis was tested in 100 alcoholics who underwent biopsy during clinical investigation. Mean values of glutamate dehydrogenase (GDH), serum aspartate and alanine transferase (SGOT and SGPT), ornithine carbamoyltransferase (OCT), and gamma-glutamyltranspeptidase (gamma-GTP) tended to rise with increasing liver cell necrosis, though values of SGOT, SGPT, OCT, and gamma-GTP showed considerable overlap between the 32 patients with histologically proved hepatitis and the 68 without. By contrast, GDH values showed virtually no overlap between patients with and without hepatitis, and a value of two and a half times the normal value discriminated between the two groups.**

**Because of its easy determination and its reliable reflection of liver cell necrosis the GDH concentration should be estimated routinely in alcoholic patients.**

## Introduction

Liver cell necrosis is considered to represent an important factor in the progression of liver disease. Since repeat biopsies are impracticable for monitoring purposes, spill-over into the blood of the so-called liver enzymes, especially transaminases, is commonly used as a marker of liver cell necrosis. In the follow-up of patients with alcoholic liver disease, however, this approach has proved to be unsatisfactory. Blood transaminase concentrations are a poor reflection of liver cell necrosis.[1] In alcoholic hepatitis, for example, concentrations of transaminases are only moderately raised and normal values are occasionally found.[2] Moreover, transaminases are not liver-specific and raised concentrations may reflect, at least partly, damage to other organs. $\gamma$-Glutamyltranspeptidase ($\gamma$-GTP) was recently suggested to be a useful marker of alcoholic liver disease.[3] But although there is some correlation between raised $\gamma$-GTP concentrations and liver cell necrosis,[4] raised concentrations may reflect only microsomal induction by alcohol in some cases,[5-7] and increases produced by non-hepatic causes are common.

In an attempt to find a more suitable marker of liver necrosis in alcoholics, we focused on glutamate dehydrogenase (GDH) for various reasons. Firstly, it occurs predominantly in the liver, where its concentration (U/g protein) is 17 times that found in heart muscle, 80 times that found in skeletal muscle, and 28 times that found in pancreas.[8] Secondly, its activity is 1·7 times greater in the centrolobular part of the liver, where alcoholic liver injury produces its major effects,[9] than in the peripheral portion of the liver lobule. Thirdly, the enzyme is exclusively intramitochondrial, and mitochondrial damage due to alcohol has been documented.[10]

We tested the usefulness of GDH values in alcoholics by correlating the degree of liver cell necrosis with the blood enzyme value determined on the day of biopsy. Results were compared with those determined by estimating concentrations of conventional enzymes.

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