Peptic ulceration, gastric secretion, and renal transplantation

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Summary

Fifty-four patients on haemodialysis for chronic renal failure underwent renal transplantation. Basal and maximum acid output and the incidence of peptic ulcer before transplantation were not significantly different from those of controls. But after renal transplantation the incidence of symptoms of peptic ulcer was high (22%) and four out of six patients who developed gastrointestinal bleeding died from this complication.

In men peak acid output was significantly increased after renal transplantation and was associated with a 30% incidence of symptoms of peptic ulcer compared with 10% in women, who showed no significant change in mean basal or peak acid output. Peptic ulceration after transplantation was not associated with steroid dosage, hyperparathyroidism, or the height of blood urea concentrations.

Given criteria of a history of dyspepsia, abnormal barium meal findings, or gastric hypersecretion, it was not possible to identify patients at risk from peptic ulceration or life-threatening complications after renal transplantation. Thus the routine screening of these patients for peptic ulcer has no practical value, and the incidence of fatal complications is not high enough to justify routine prophylactic anti-ulcer surgery aimed at reducing acid secretion before renal transplantation.

Introduction

A patient who has had a renal transplant may develop severe dyspepsia, gastrointestinal perforation, or bleeding, all of which carry a high mortality. In one series of 140 transplant patients upper gastrointestinal bleeding occurred in 14 patients, all of whom died despite surgery.[1] In another series of 184 patients with transplants only one out of six with bleeding survived.[2] Because these complications have such a poor prognosis efforts have been made to detect patients with abnormal gastric acid secretion.[3] It has been claimed that those at risk can be identified so that prophylactic gastric surgery might be performed before renal transplantation.[4]

We reviewed our patients who had undergone renal transplantation to determine (*a*) the incidence of dyspepsia, gastrointestinal perforation, and bleeding; (*b*) the morbidity and mortality from these complications; and (*c*) basal and maximum acid secretion before and after transplantation. From these data we attempted to identify those patients at risk and assess whether the morbidity and mortality rates justify prophylactic gastric surgery before transplantation.

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Patients and methods

Fifty-four patients (22 women and 32 men) were followed for six months to seven years after renal transplantation. All had undergone regular haemodialysis for 20-24 hours each week before the operation. The following observations were made.

Clinical state—Gastrointestinal symptoms were sought regularly and documented before and after transplantation.

Barium studies—Thirty-five of the 54 patients, including all those with dyspeptic symptoms, underwent barium meal examination before transplantation.

Gastric acid secretion studies—Each patient underwent acid secretion studies before transplantation; 25 were studied again at least six weeks after the operation and when immunosuppressive treatment had reached maintenance levels (azathioprine 2 mg/kg/day and prednisone 15 mg/day). In patients studied before 1967 basal acid output and maximum acid output were measured. After overnight fasting for 10 hours a nasogastric tube was positioned fluoroscopically in the most dependent part of the stomach, the resting juice discarded, and the basal acid output (in mmol/h) determined in four successive 15-minute samples. At the end of this basal period 0·04 mg of histamine acid phosphate/kg body weight/hour was infused continuously until a secretory plateau was reached. The plateau acid output was then calculated (in mmol/h) as the sum of the four highest successive 15-minute outputs.[5] Titratable acidity was measured to pH 7 with a pH meter or automatic titrator.

Patients studied since 1967 had their basal acid output assessed in a similar manner, but, instead of plateau acid output, peak acid output was measured during the hour after an intramuscular injection of pentagastrin (6 μg/kg body weight). Four 15-minute fractions of gastric secretion were collected and the sum of the two highest consecutive acid outputs was multiplied by two to give peak acid output in mmol/h. In this report we took the earlier plateau acid output values to approximate to the peak acid output PAO value, and all maximum acid outputs are referred to as peak acid output. Statistical comparisons between basal and peak acid outputs before and after transplantation were calculated by the Wilcoxon matched-pairs ranked sign test.

Other factors—We examined the relationship of age, sex, steroid dosage, blood urea concentration, secondary hyperparathyroidism, and blood group to the incidence of peptic ulcers after transplantation.

Results

Clinical status—Nine patients (17%) had symptoms suggestive of peptic ulceration before transplantation. All were treated conservatively by diet and alkalis and all made a satisfactory recovery. Eventually these patients received a renal transplant and only three of these nine patients had any symptoms of peptic ulcer after transplantation (table I). These were easily controlled by conservative measures. Nine further patients who had not had dyspepsia developed symptoms within three months after transplantation. Six of these patients had gastrointestinal bleeding and four died as a result of this (table I). Two of these patients underwent gastric surgery for bleeding and both died. At necropsy two of the four patients had both gastric and duodenal ulcers, the third showed oesophageal ulcers, and the fourth had massive gastric haemorrhage with possible bleeding points.

Barium studies—Thirty-five of the 54 patients underwent a barium meal examination and in five the results were abnormal (table I). All these patients received conservative treatment and their symptoms responded satisfactorily. Four of the six patients who bled after transplantation had no peptic ulcers on barium studies; the other two were not studied. Endoscopy was not carried out routinely in these patients and only one of those who bled after transplantation underwent gastroscopy.

Gastric acid secretion studies—The results of gastric acid secretion studies in men and women before transplantation were compared with those of control groups of 20 men and 20 women[6] (fig 1). There were

TABLE I—*Details of patients with symptoms of peptic ulcer before transplantation*

Case No	Sex	Symptoms and signs before transplant	Barium meal findings before treatment	Symptoms and signs after transplant	Outcome
Patients with symptoms of peptic ulcer before transplantation					
1	M	Bleeding	Normal	None	Satisfactory
2	M	Bleeding	Duodenal spasm	None	Satisfactory
3	M	Pain, reflux	Hiatus hernia	None	Satisfactory
4	M	Pain, reflux	Normal	None	Satisfactory
5	F	Pain, reflux	Normal	None	Satisfactory
6	F	Pain	Duodenal ulcer	None	Satisfactory
7	M	Pain, reflux	Hiatus hernia	Pain, reflux	Satisfactory
8	M	Pain	Normal	Pain	Satisfactory
9	M	Bleeding	Normal	Pain	Satisfactory
Patients with symptoms of peptic ulcer after transplantation					
10	M	None	Normal	Bleeding	Satisfactory
11	M	None	Normal	Pain	Satisfactory
12	M	None	Normal	Pain	Satisfactory
13	M	None	Duodenal diverticulum	Bleeding	Satisfactory
14	M	None	Not done	Pain	Satisfactory
15	M	None	Not done	Bleeding	Died
16	M	None	Not done	Bleeding	Died
17	F	None	Normal	Bleeding	Died
18	F	None	Normal	Bleeding	Died

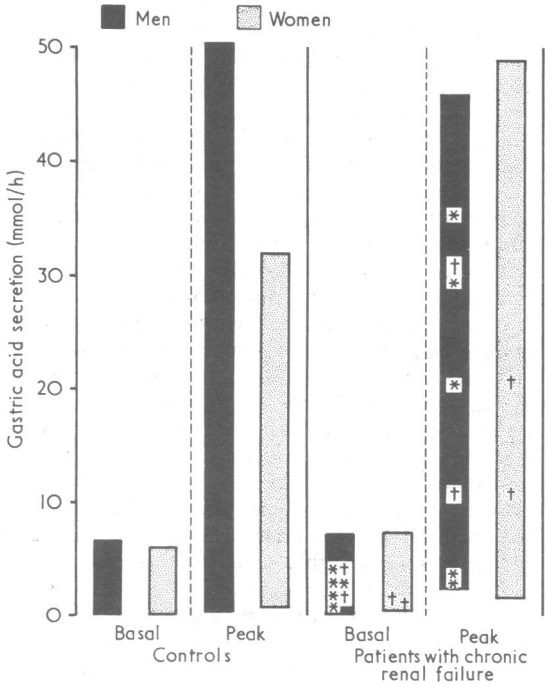

FIG 1—Range of basal and peak acid output in 40 men (20 controls and 20 with chronic renal failure) and 40 women (20 controls and 20 with chronic renal failure). *=Patients with non-fatal symptoms of peptic ulcer after transplantation. †=Patients who bled and died after transplantation.

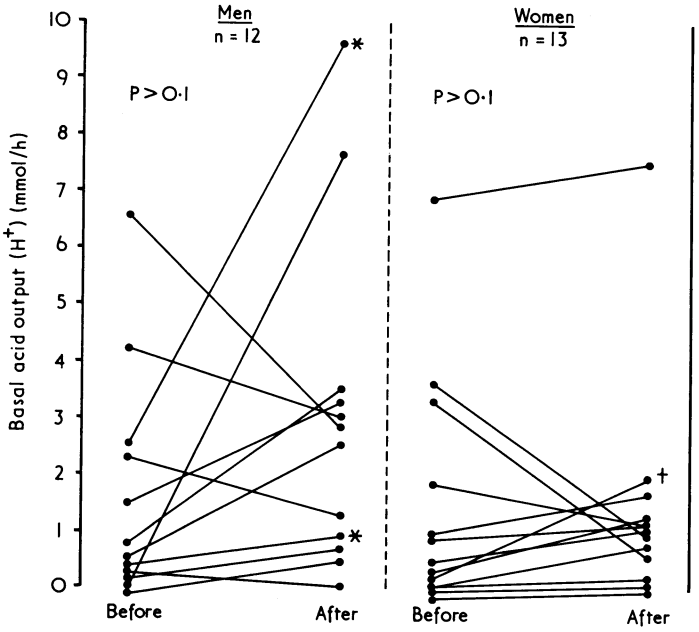

FIG 2—Basal acid output in patients before and after renal transplantation. *=Patients with non-fatal symptoms of peptic ulcer after transplantation. †=Patient who bled and died after transplantation.

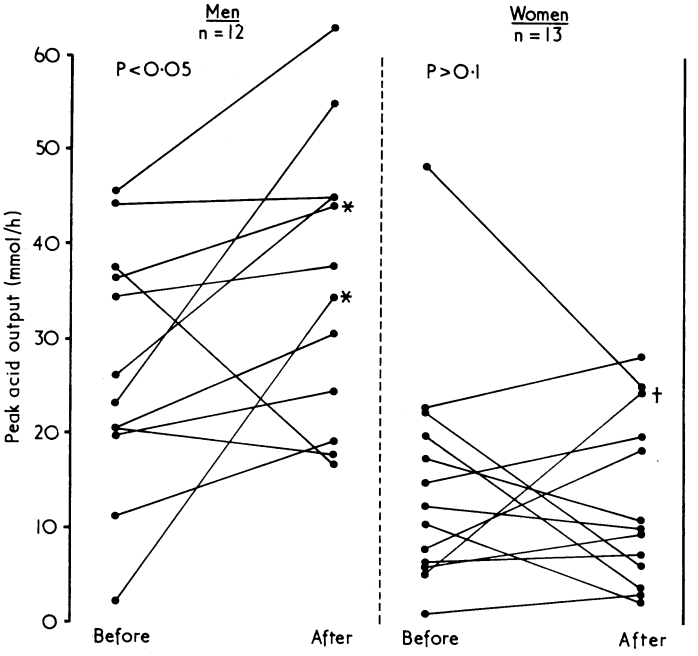

FIG 3—Peak acid output in patients before and after transplantation. *=Patients with non-fatal symptoms of peptic ulcer after transplantation. †=Patient who bled and died after transplantation.

no significant differences in the basal and peak acid output levels for these groups, although the values for patients with chronic renal failure tended to be higher than those of the controls. Twenty-five patients (12 men and 13 women) had gastric acid secretion studies repeated after transplantation. The results showed that there was an insignificant rise in basal acid output in both sexes after transplantation (fig 2). There was a significant rise in peak acid output after transplantation in men but not in women (fig 3).

OTHER FACTORS

Sex—Ten of the 32 men had symptoms of peptic ulceration after transplantation (table II). Peak and output was significantly increased after transplantation (fig 3) in these men. Two of the 22 women developed bleeding from peptic ulceration, and this was the cause of death in both (table II). There were no significant changes in acid secretion after transplantation in the women studied.

TABLE II—*Barium meal and necropsy findings in patients who developed symptoms of peptic ulcer after transplantation*

Case No	Sex	Symptoms after transplant	Barium meal findings after transplant	Necropsy findings
7	M	Pain, reflux	Hiatus hernia	
8	M	Pain	Normal	
9	M	Pain	Normal	
10	M	Bleeding	Normal	
11	M	Pain	Pylorospasm	
12	M	Pain	Duodenal scarring	
13	M	Bleeding	Duodenal diverticulum	
14	M	Pain	Normal	
15	M	Fatal bleeding	Not done	Gastric and duodenal ulcers
16	M	Fatal bleeding	Not done	Gastric and duodenal ulcers
17	F	Fatal bleeding	Inconclusive	Oesophageal ulcers
18	F	Fatal bleeding	Pyloric ulcer	Oesophageal and pyloric ulcers

Blood group—The distribution of the ABO blood groups in this group of patients was normal for the United Kingdom.[7] Too few patients developed peptic ulcers to draw conclusions about individual blood groups.

Secondary hyperparathyroidism and blood urea concentration—There was no correlation between peptic ulceration and secondary hyperparathyroidism or serum calcium and blood urea values.

Steroid dosage—There was no correlation between the steroid dose and the development of either symptoms or signs of peptic ulceration. Each of the transplanted patients, including those who developed peptic ulceration, were on maintenance steroids. Two of the six patients who bled did so within two weeks of receiving high doses of steroids for a rejection episode; neither of the patients had developed symptoms when they were receiving these high doses. The four other patients who bled had been on maintenance doses of steroids for two months, three months, four months, and two years after transplantation.

Discussion

There were striking differences in the incidence of and morbidity and mortality from peptic ulceration before and after renal transplantation in these patients. Of the nine patients who developed symptoms of dyspepsia while on dialysis, only one had a peptic ulcer shown on barium meal examination—an incidence similar to that in age-matched controls.[8] Only three of these nine had persistent dyspeptic symptoms after transplantation and these were easily controlled by conservative measures. After transplantation nine other patients developed symptoms of peptic ulceration. They had no dyspeptic history, but four subsequently died from gastrointestinal bleeding.

We examined the possibility that routine gastric acid secretion studies before transplantation would predict those patients who might be at risk. In our earlier study of gastric acid secretion before and after transplantation we suspected that this test had little predictive value,[3] and we have confirmed this impression in this larger study. Although the peak acid output levels were raised in most men after transplantation it was not possible to identify those at risk from either bleeding or perforation. Those patients with high basal and peak acid output levels before transplantation did not prove to be specially at risk.

The findings of different investigators vary considerably and the evidence for abnormal gastric acid secretion in chronic renal failure remains inconclusive. Ventkateswaran *et al*[9] compared 16 patients with chronic renal failure (10 on regular haemodialysis) with eight normal controls. They found a high mean peak acid output of 33·6 mmol/h in those with chronic renal failure. They did not, however, distinguish between male controls, some of whom had similar peak acid output values, and women controls, among whom such values would have been high.[6] They found that six patients had abnormal barium meal findings and four of these showed peptic ulceration on at least one occasion—an incidence of 25%. Shepherd *et al*[10] reported studies in 15 patients with chronic renal failure and found a mean peak acid output in the normal range, but the basal acid output was higher (5 mmol/h) in six patients, although the mean basal acid output was not reported. Nine of the 15 patients had proved peptic ulceration.

In a study of 56 patients awaiting transplantation[4] 18% of the men had achlorhydria, while the mean peak acid output in women was significantly raised in response to pentagastrin stimulation. Fillastre *et al*[11] and Dorph *et al*[12] showed that the maximal response to histamine in patients with chronic renal failure was within the normal range, and Goldstein *et al*[13] found a high incidence of peptic symptoms among seven patients on haemodialysis; there was also a high basal acid output but no increase in gastric secretion in response to betazole stimulation. Canavan *et al*[14] found abnormally high basal and peak acid outputs in response to pentagastrin in 10 patients on chronic dialysis with no significant change after transplantation. McConnell *et al*[15] attributed the low basal and peak acid outputs in some patients with chronic renal failure to uraemic gastritis and found a significant rise after transplantation.

In our present study the basal and peak acid outputs of the patients with renal failure were not significantly different from control values. These normal acid results in patients with chronic renal failure are consistent with our findings of an incidence of peptic ulceration within the normal range for a control population. In only one other series of a similar size to ours the incidence of peptic ulceration was almost identical with ours (9% compared with 8%).[4] Other reported series have included fewer patients. Gastrointestinal haemorrhage, once a common complication of chronic renal failure, is now rarely seen and this may be attributed to effective dialysis and the absence of the qualitative defect in platelets that previously occurred in these patients.[16]

Our study has shown that the barium studies had no predictive value. All those with abnormal findings before transplantation received conservative treatment and their symptoms responded satisfactorily. Four of the six patients who bled after transplantation had no abnormality shown on the barium meal examination carried out before transplantation; the other two patients were not studied. When duodenal ulceration occurred after renal transplantation it was often associated with gastric and oesophageal ulceration, and this was seen in both the barium meal and the necropsy findings of the 12 patients who developed peptic ulceration after transplantation (this includes the nine patients with no dyspeptic disease before transplant). Lewicki *et al*[17] have suggested that this reversal of the usual gastroduodenal location of ulcers is evidence that topical steroids may be important aetiological agents.

Our findings agree with those of others on the high incidence of and considerable morbidity and mortality from peptic ulcer disease after renal transplantation. The incidence of peptic disease in our series was 22%, and half the cases were complicated by bleeding, and four of the six patients died.

This increased incidence is usually considered to result from a combination of stress and immunosuppressive drugs. The steroids used in the post-transplant period may be ulcerogenic either by impairing mucosal resistance or by increasing peak acid output, as seen in men in this study. Aubrey and Burns[18] have shown in dogs that steroids applied topically to vagally denervated fundic pouches caused increased acid outputs. Spiro and Miles[8] noted that the incidence of peptic ulceration in patients with rheumatoid disease who were not taking steroids was comparable to that in the general population (under 10%). But in a well-controlled study of 177 rheumatoid patients receiving steroids the incidence was 71% with a male to female ratio of 3:1, and this sex bias is similar to that observed in our present study. Spiro and Miles[8] concluded that in susceptible subjects ACTH and steroids will stimulate gastric hypersecretion, but such patients cannot easily be predicted. This conclusion supports our finding that on current criteria the patients who would benefit from prophylactic surgery cannot be identified.

Conclusion—We conclude that preoperative symptoms, barium meal examinations, and acid studies cannot predict those patients with renal failure who will develop gastrointestinal ulceration and bleeding after renal transplantation. Although four of the 54 transplant patients died of these complications, we do not consider that routine prophylactic anti-ulcer surgery aimed at reducing gastric secretion is justified before renal transplantation. The routine administration of a safe antisecretory drug might be possible.

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Persistent measles infection in malnourished children

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Summary

Thirty malnourished and 25 well-nourished children were studied six to 31 days after the onset of a measles rash. Evidence of the virus was found in 40% of the malnourished children but in none of the well-nourished controls. Giant cells were found in the nasal secretions of five out of 17 malnourished children and measles antigen was detected in the lymphocytes of eight out of 28. The malnourished children showed depressed cell-mediated immunity to measles and candida antigens and a low response to meningococcal vaccine. Fifteen died from intercurrent infections. Malnutrition was thought to have depressed the immune response in these children, resulting in a severe and prolonged attack of measles. This, in turn, led to further damage to the immune system and more severe malnutrition. Thus these children were made susceptible to intercurrent infection.

Introduction

Measles in tropical countries is often severe, especially in children who develop a dark desquamating rash.[1] Such children may lose much weight and take up to three months to regain it. Scheifele and Forbes in Kenya showed that these children continued to excrete giant cells for an average of 12 days after the appearance of the rash.[2] On this evidence they suggested that measles infection persisted longer in malnourished children.

In Zaria, where this syndrome of severe measles is common, we looked for persisting measles virus in children who were malnourished after measles, because we thought that their disease might be due to persistence of the virus. We report here evidence that there is indeed persistent virus in malnourished children after measles.

Patients and methods

Thirty children who had had a measles rash for over one week and who were not recovering normally were studied. The mean duration between the onset of the rash and the time of presentation was 13 days (range 6-31 days) and the mean age ($\pm$1SD) of the children was 22 ± 10 months. All of these children were weak and anorectic and had diarrhoea; 13 had bronchopneumonia; six had oral candidiasis; and eight others had ulcerative stomatitis. Ten had had a severe rash, in which widespread skin desquamation had occurred. Eleven were underweight, 11 were marasmic, five had marasmic kwashiorkor, and three had kwashiorkor.[3] The overall mortality in this group was 50% despite intensive treatment in hospital and nutritional advice to the mother on discharge.

Twenty-five well-nourished children who had recovered normally from measles were also studied as controls. Their mean age was 19 ± 13 months and they had had measles on average 12 days earlier (range 7-20 days). None had any secondary infections and none died. The nutritional data for the two groups are shown in table I. The patients were clearly stunted and malnourished compared with the controls.

Patients and controls were vaccinated with meningococcal group C vaccine (Institut Merieux) and *Salmonella typhi* vaccine (Burroughs Wellcome), and blood for antibody assay was taken 14 days later.

TABLE I—*Nutritional measurements in patients and controls two to four weeks after measles. Values are means* $\pm$*1SD*

	Patients (n = 30)	Controls (n = 25)	P
Weight for age (% Harvard standard) ..	60 ± 11	91 ± 7	<0·01
Height for age (% Harvard standard) ..	90 ± 6*	97 ± 3	<0·01
Arm circumference for age (% Harvard standard)	75 ± 8	97 ± 7	<0·01
No with oedema	8	0	<0·02
Serum albumin (g/l)	23 ± 10	30 ± 7	<0·01
Serum transferrin (% normal adult standard)	37 ± 26	76 ± 28	<0·01

*Below 3rd percentile of standard for British children.[18]

Haemagglutinating and neutralising antibodies to measles were measured by standard microtitre techniques, Vero cells being used in the neutralisation test. Meningococcal antibodies were measured by microtitre haemagglutination[4] and antibodies to the O antigen by *S typhi* by a microtitre method. Serum albumin concentration was measured using bromcresol green[5] and serum transferrin concentration by the Mancini method, using a monospecific antiserum.

Detection of virus and viral antigens—Cells from nasal secretions[6] and from lymphocyte culture were stained with 0·1% acridine orange and examined by fluorescent microscopy for the presence of giant cells. Lymphocytes obtained by defibrination and sedimentation in 3% dextran were cultured at 1×10^6 cells/ml in RPMI medium with 10% fetal calf serum and phytohaemagglutinin, which was added at an optimal concentration of 5 mg/l, in flat-bottomed microtitre plates. After three days cells were harvested, and some cells and supernatant were stored at -30°C for later viral culture. The rest of the cells were centrifuged and an indirect immunofluorescence test for measles antigen was performed by incubating them with convalescent measles serum and then counter-staining them with an anti-whole immunoglobulin conjugate. In most cases cells from a patient with acute measles, a control patient, and an adult volunteer were cultured simultaneously,

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