Gastroduodenal Complications in Kidney Transplant Recipients

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Oral antacids taken every two hours while awake provided the only prophylaxis against gastroduodenal ulceration for 167 kidney transplant recipients between 1968 and July 1978. Either perforation or major hemorrhage occurred in eight patients within 30 days after transplantation. Between July 1978 and January 1981, bleeding occurred within 30 days in two of 147 recipients who were treated with both antacids and cimetidine. Of the 147 patients, eleven with a history of ulcers had undergone pretransplant vagotomy; neither perforation nor hemorrhage occurred in any of the eleven patients. Despite reports that cimetidine enhances certain types of immune responses, we observed slightly greater graft survival in the group treated with cimetidine.

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GASTRODUODENAL ULCERATION frequently complicates the management of patients with end stage renal disease while they are on chronic hemodialysis and after kidney transplantation.[1-4] The incidence of hemorrhage or perforation within three months after transplantation varies from 25%, in early reports, to less than 5%, in recent years.[5,6] Because of concomitant immunosuppression, the potential for sepsis and the frequent need to continue dialysis during periods of transient renal dysfunction, the risk of death after perforation and hemorrhage in this chronically ill population approaches 50%.

Factors that predispose transplant recipients to ulceration include high dose corticosteroid therapy and hypergastrinemia. Gastrin is degraded in the normal renal cortex and is not removed readily by hemodialysis. All anephric patients and between 50–75% of patients with chronic renal failure have high concentrations of serum gastrin.[7,8] Despite high gastrin concentrations, most have low basal gastric acid output, presumably because acid is neutralized by gastric juice ammonia derived from plasma urea secreted into the stomach, and acted on by gastric urease. Peak acid output, in response to pentagastrin stimulation, is high in anephric patients, and in the high normal range for patients with chronic renal failure.

Attempts to prevent or control ulceration have concentrated on neutralizing and suppressing the output of gastric acid. Antacid therapy after transplantation and pretransplant vagotomy for patients with a history of gastritis or ulcer have reduced significantly the incidence of gastroduodenal ulceration in kidney recipients.[5] Except perhaps for patients with a history of ulcers or gastritis, antacids alone, if used vigorously with pH monitoring, might be sufficient.[9] However, prolonged use of high dose prednisone and varying degrees of renal dysfunction leave the transplant recipient at relatively high risk for ulcer formation or gastritis for several months. Monitoring of gastric pH is applicable only for the first few days, and prolonged compliance with a vigorous antacid regimen is difficult for many patients. The likelihood of achieving adequate control of gastric acid might be increased by adding the histamine H-2 antagonist cimetidine to the antacid regimen. However, reports that cimetidine augments delayed type hypersensitivity reactions and a variety of cell mediated immune responses *in vitro* have deterred many centers from using it to treat transplant recipients.[10-12]

Between 1968 and July 1978, we encountered serious gastroduodenal bleeding or perforations within 30 days after kidney transplantation in eight of 167 patients treated with antacids alone every two hours while awake. Since July 1978, we have added cimetidine to the prophylactic regimen and have required pretransplant vagotomy in patients with documented histories of upper gastrointestinal ulceration or hemorrhage. Early posttransplant bleeding has occurred in two of 136 patients without prior ulcer or bleeding history, and in none of 11 patients who had undergone pretransplant vagotomy. The addition of cimetidine did not reduce graft survival.

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TABLE 1. *Gastroduodenal Complications within 30 Days for 167 Recipients from 1968 to July 1978 (Prophylaxis: Antacids Only)*

Year	Gastrointestinal Complication	Other Complications	On Dialysis at Time of Bleed	Blood Transfusion	Emergency Surgery	Outcome
1968	Erosive gastritis	Sepsis, rejection	No	4 units	No	Death
1975	Duodenal ulcer, erosive gastritis	Sepsis	Yes	50 units	Yes	Death
1975	Duodenal ulcer	Rejection	Yes	3 units	No	Survived
1975	Erosive gastritis	Sepsis	No	12 units	No	Survived
1977	Perf. gastric ulcer	Rejection	No	No	Yes	Survived
1977	Erosive gastritis, pyloric ulcer	Rejection	Yes	40 units	Yes	Survived
1978	Erosive gastritis, perf. gastric ulcer	Sepsis	No	6 units	Yes	Death
1978	Erosive gastritis	Rejection, sepsis	Yes	12 units	No	Death

Methods

This report includes all kidney transplant recipients at The University of Chicago Hospitals between July 1968 and January 1981. The median age of the patients was 33 years; 60% were white and 51% were male. The administration of azathioprine and prednisone followed the standard regimens for baseline immunosuppression and treatment of organ rejection.[13] Beginning in 1972, antilymphocyte globulin, prepared in goats and rabbits against cultured lymphoblasts, was injected subcutaneously in doses as high as 20 mg/kg body weight for the first seven posttransplant days. Between 1975 and 1978, recipients of cadaveric kidneys were entered into a prospective study to evaluate pretransplant splenectomy.

Throughout the entire observation period, from July 1968 to January 1981, all patients were instructed to take oral antacids (aluminum hydroxide 200–400 mg and magnesium hydroxide 200–400 mg) every two hours, while awake, for the first six weeks after transplantation. The pH of gastric aspirate was not monitored or maintained above 3.5 unless upper gastrointestinal bleeding occurred. Beginning July 1978, all patients received cimetidine for the first three months after transplantation. It was administered intravenously for the first two days and then by mouth in doses of 300 mg every six hours (every 12 hours if dialysis was still required). Between 1968 and July 1978, patients with histories of peptic ulcer or bleeding were urged but not required to undergo pretransplant vagotomy. Since July 1978, no patient with a history of ulcer or bleeding has received a transplant without prior vagotomy.

Patients who bled enough to require transfusion underwent endoscopic and barium swallow x-ray examinations to determine the cause of bleeding. For purposes of this review, only gastroduodenal perforation or hemorrhage requiring transfusion of at least two units of blood were considered to be serious complications.

The chi square test was used to evaluate the statistical significance of severe bleeding and other complications of gastroduodenal ulceration in the two groups of patients, before and after July 1978. The per cent graft survival was calculated on the basis of life tables.[14]

Results

Between 1968 and July 1978, the course of eight out of 167 kidney transplant recipients was complicated within the first 30 days by gastroduodenal perforation or hemorrhage requiring more than two units of blood (Table 1). Oral antacids administered every two hours while awake provided the only prophylaxis against ulceration. Hemorrhagic erosive gastritis was present in six patients. Of these six patients, two also had pyloric or duodenal ulcers and five were septic. All four deaths occurred in the patients with sepsis. Half of the patients were still being maintained in hemodialysis at the time of the ulcer complication. The need for heparin during hemodialysis treatments aggravated the course of two patients with the most severe hem-

TABLE 2. *Gastroduodenal Complications within 30 Days for 136 Recipients without Ulcer History from July 1968 to January 1981 (Prophylaxis: Antacids and Cimetidine)*

Year	Gastrointestinal Complication	Other Complications	On Dialysis at Time of Bleed	Blood Transfusion	Emergency Surgery	Outcome
1978	Antral ulcer erosive gastritis	None	Yes	15	No	Survival
1979	Erosive gastritis	None	Yes	13	No	Survival

TABLE 3. *Absence of Gastroduodenal Complications within 30 days for 11 Recipients with History of Ulceration (Prophylaxis: Antacids, Cimetidine and Vagotomy)*

Prior Gastrointestinal History	Operation			Kidney Donor		Normal Graft Function Beyond 3 Months
	Highly Selective Vagotomy	Vagotomy Pyloroplasty	Vagotomy Antrectomy	Related	Cadaver	
Gastric ulcer	X				X	Yes
Duodenal ulcer	X				X	Yes
Duodenal ulcer	X				X	Yes
Duodenal ulcer	X			X		Yes
Duodenal ulcer	X				X	No (rej)
Duodenal ulcer		X			X	Yes
Bleeding duodenal ulcer		X			X	Yes
Duodenal ulcer		X		X		Yes
Duodenal ulcer		X			X	Yes
Duodenal ulcer		X			X	Yes
Duodenal ulcer			X		X	Yes

orrhage (40 units and 50 units) from gastritis. Only two patients had a pretransplant history of ulcer disease. One underwent pretransplant vagotomy and pyloroplasty and had no ulcer related complications after transplantation. The other, without vagotomy, died from posttransplant erosive gastritis, perforated gastric ulcer, and sepsis.

In July 1978, cimetidine (300 mg administered every six hours) was added to the antacid regimen. Of 136 transplant recipients without histories of ulcer disease, two developed hemorrhagic erosive gastritis; both still required maintenance hemodioalysis because of temporary renal dysfunction and both survived with eventual good renal function (Table 2). Chi square analysis indicated no significant difference for the incidence of gastroduodenal complications between the groups treated with antacids alone or antacids with cimetidine. Beginning in July 1978, pretransplant vagotomy was required for all patients with a history of gastroduodenal ulcer. Five patients underwent highly selective vagotomies, five had truncal vagotomies and pyloroplasties, and one had truncal vagotomy and antrectomy (Table 3). All eleven patients received antacids and cimetidine in the posttransplant course, and none has had further ulcer complications.

In addition to the ten patients whose gastroduodenal complications occurred within 30 days after transplantation (Tables 1 and 2), seven of 314 recipients have had later ulcer or gastritis complications at a time when function in the grafted kidney was normal or nearly so (Table 4). No patient had a pretransplant history of gastroduodenal ulcer disease. Six of the seven complications occurred within the first 18 months after transplant; the seventh, a duodenal perforation, occurred after ten years. Three of the seven patients died. Sepsis preceded hemorrhagic gastritis in two patients and followed perforation of a duodenal ulcer in the third.

Modest changes were made in the immunosuppressive regimen between 1968 and 1975, but it was constant between January 1975 and January 1981. A prospective study to evalute pretransplant splenectomy in recipients of cadaveric kidney transplants was conducted between 1975 and July 1978. Between 1975 and July 1978, half (24/49) of the recipients of first cadaveric kidney grafts had undergone pretransplant splenectomy. Because splenectomy was shown to increase graft survival, it became standard practice and was performed in 92 out of 96 patients, who received their cadaveric kidneys between July 1978 and January 1981. Table 5 shows that there is no significant difference for

TABLE 4. *Gastroduodenal Complications after 30 Days in Recipients with Functioning Kidney* (314 Transplants 1968–1961)*

Gastrointestinal Complication	Blood Transfusion	Posttransplant Interval	Concurrent Other Complication	Emergency Surgery	Outcome
Perforated duodenal ulcer	No	6 mo	—	Closure	Death
Duodenal ulcer	24 units	8 mo	Hepatitis	Pyloroplasty	Survived
Erosive gastritis	6 units	14 mo	Sepsis	No	Death
Antral ulcer	8 units	14 mo	Sepsis	Vagotomy and antrectomy	Death
Erosive gastritis	6 units	18 mo	Alcohol abuse	No	Survived
Duodenal ulcer	6 units	18 mo	—	No	Survived
Perforated duodenal ulcer	No	10 yr	—	Closure	Survived

* None had history of prior gastroduodenal complications.

TABLE 5. *Cimetidine and Survival of First Cadaveric Kidney Grafts after Splenectomy*

	1975–July 1978 No Cimetidine 24 Transplants	July 1978–Jan. 1981 Cimetidine 92 Transplants	
	Per Cent Functioning	Per Cent Functioning	p
6 months	71	75	0.69
1 year	63	73	0.31
2 years	54	65	0.36

graft survival in splenectomized recipients of first cadaveric kidneys between the antacid only group (January 1975 to July 1978) and the antacid + cimetidine group (July 1978 to January 1981).

Discussion

There seems to be general agreement that gastric acid secretion is an essential causative factor for peptic ulceration and erosive gastritis in stressed high risk patients.[15] Vigorous antacid treatment, with careful monitoring of gastric juice to ensure pH close to neutrality, can probably prevent most if not all complications of gastroduodenal ulceration.[9] Several reports suggest that cimetidine is as effective as antacids, but pH monitoring may also be important if maximum benefit is to be derived from cimetidine.[16–20] The dose of cimetidine required to suppress gastric acid formation varies widely, especially in critically ill and septic patients.[19] Because cimetidine, a histamine H-2 antagonist, reduces gastric acid production, while antacids only neutralize acid that has already been secreted, treatment with the combination is appealing, especially for transplant recipients who are ambulatory and eating within a few days, but remain at high risk for ulcer complications for weeks or months. Statistical analysis showed that the incidence of ulcer complications in our antacid group (8/167) was not different from our antacid plus cimetidine group (2/147). Prophylactic cimetidine appears not to have benefited the transplant recipients without prior ulcer problems between July 1978 and 1981. The apparent reduction of gastroduodenal bleeding in that group may be attributable to less posttransplant sepsis. Since 1973, we have tended, steadily, to treat fewer rejection episodes, and to limit the total dose of corticosteroids used to treat rejection. There were only four deaths during the first posttransplant year among the 96 recipients of first cadaveric kidneys in the prophylactic antacid plus cimetidine group; causes of those four deaths were pancreatitis in one and pulmonary sepsis in three patients.

Although cimetidine may not have been important for the 136 patients with no history of ulcer disease, it may have helped to prevent recurrent ulcer complications after transplantation in the 11 patients with known ulcer histories who underwent pretransplant vagotomy and subsequently received both antacids and cimetidine after transplantation. Antacids alone may have been insufficient in the six patients whose pyloroplasty or antrectomy might not have allowed long enough retention of antacids in the stomach. Because of the great likelihood of posttransplant ulcer complications in those with a known ulcer history, we support the position of others that prophylaxis should include pretransplant vagotomy and the administration of posttransplant antacids; we will probably also continue to administer cimetidine at least to these high risk patients and to any others who become septic or develop gastroduodenal ulceration, despite antacid prophylaxis.

The concern that cimetidine might increase graft rejection seems to be unwarranted. Histamine receptors are present on many different types of cells within the immune system.[21] The effects of cimetidine on the immune system may be balanced in such a way that the likelihood of rejection is not affected. Moreover, at least two reports indicate that cimetidine prolongs skin graft survival rates in rats.[10,21] In addition, three separate clinical reports on prophylactic use of cimetidine in a total of 66 transplant recipients indicated no increased incidence of rejection.[22–24] Our experience with prophylactic cimetidine in 147 transplant recipients pointed if anything toward less, not more, rejection. There seems to be no clinical basis for withholding cimetidine from transplant recipients.

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Discussion

Dr. Olga Jonasson (Chicago, Illinois): Upper gastrointestinal bleeding in the transplant recipient is unusual in the absence of sepsis, rejection, or both. The ulceration that occurs during the septic episode is most commonly of the erosive gastritis type, not at all unlike the stress ulceration seen in patients with postoperative sepsis due to a variety of factors. The value of cimetidine has been questioned in patients with stress ulceration in association with sepsis, and antacids have been more reliably effective.

The upper gastrointestinal hemorrhage seen in patients with rejection may also include more typical peptic ulcer disease, complicated by periodic anticoagulation and by uremia. In these patients, especially those with a history of peptic ulcer disease, cimetidine may, in fact, be the optimal prophylactic therapy.

Therefore, I would ask Dr. Stuart if he believes that the reduction in upper gastrointestinal bleeding episodes he has observed in recent years can really be attributed to cimetidine prophylaxis, or, instead, may it be credited to an overall reduction in the incidence of post-transplant sepsis, as we have become more knowledgeable in the management of the transplant recipient, both before and after operation.

Dr. Stuart, if you were to do a prospective, randomized study today comparing antacids and cimetidine as the only means of prophylaxis of upper gastrointestinal bleeding, what would you predict the outcome of such a study would be?

Dr. Arnold G. Diethelm (Birmingham, Alabama): This is a particularly important subject, since the morbidity and mortality rates of patients with upper gastrointestinal bleeding are well known to those involved in renal transplantation.

As noticed by Dr. Stuart, it is essential that early, aggressive diagnostic measures be initiated in the course of bleeding, including endoscopy and gastrointestinal contrast studies.

Having reviewed the manuscript, I agree with his thesis that approximately 4 units of bleeding in the first 24 hours is an indication for surgical intervention, and if, in fact, gastroduodenal ulceration is present, then I favor pyloroplasty and vagotomy.

However, the most serious sequence of events involves patients with severely impaired renal function after transplantation caused by rejection or acute tubular necrosis and with sepsis. This group has a particularly high mortality, and requires early operation and, in many instances, prompt removal of the allograft and discontinuation of immunosuppressive therapy.

My early experience, from 1968 to 1975, was similar to that reported today. However, in the past two calendar years, I have had a consecutive series of 207 patients, and only one patient had gastroduodenal ulceration. This patient had a gastric ulcer, and probably had the lesion before transplantation.

My associates and I have not used cimetidine. We have used the usual antacid protocol, and therefore upper gastrointestinal bleeding in our current experience appears to be a minimal issue.

The central question raised by Dr. Stuart relates to whether or not cimetidine is of value in decreasing complications of gastroduodenal ulceration in the early posttransplant course. If it is, then this would be of considerable importance. However, the question is whether or not the use of cimetidine is truly cause and effect in regard to his findings.

I too, like Dr. Jonasson, wonder if a randomized, prospective study would be of help in solving the problem.

I think the most important contribution in the prevention of this problem has been limiting the total dose of steroids, early graft removal, and avoid sepsis if at all possible.

Dr. Richard E. Wilson (Boston, Massachusetts): Gastroduodenal complications occur in patients not only with kidney transplants, but in a whole variety of immunosuppressed individuals. For the surgeon, however, the transplant patient presents an ideal model to investigate the possibility of controlling these problems, since he or she has an opportunity to see these patients and manage them before they receive their drug therapy, this is not so with many other conditions.

Chronic uremia per se is associated with increased gastrin levels and abnormal clotting capabilities. Corticosteroids affect protective mucus production and the gastric mucosal barrier of parietal cells, while antimetabolites interfere with the repair process of any mucosal injury. It is no wonder that gastrointestinal bleeding and ulceration should occur more frequently in these patients. Patients with a known ulcer diathesis are even at higher risk, as Dr. Stuart pointed out.

Dr. Stuart has demonstrated the value of a vigorous prophylactic approach to this predictable problem, as have surgeons in most other groups. In 1972, we began doing vagotomy and pyloroplasty for all patients with known ulcer history, and it, too, produced a remarkable reduction in gastrointestinal complications.

It is clear that cimetidine plus antacids with vagotomy produced the best results for short- and long-term control in patients with known ulcer history. However, as the other two discussers have pointed out, is cimetidine added to antacids for people without ulcer history better than antacids alone, and is cimetidine plus antacids with vagotomy necessary for persons who have a known ulcer history? Dr. Stuart has not really proved that.