Summary

Gastroduodenal ulceration occurred in 45 patients during the post-transplantation period in a series of 500 transplantations on 434 patients. The mortality rate of this complication was high, 42%. Bleeding and perforation were the main problems. These complications occurred frequently during treatment for acute rejection. Present day prophylaxis, which is based on the use of antacids, seems to be inadequate for controlling these complications. Other possibilities for reducing the incidence of gastroduodenal ulceration in transplant patients are discussed. Since increased serum gastrin concentrations are often observed in these patients, prophylactic treatment should be based on preoperative evaluation of gastric secretion and serum gastrin determinations. The new histamine (H₂) blocking agents should be evaluated in these patients.

Introduction

Several reports¹-⁶ have indicated that peptic ulceration is a frequently observed, life-threatening complication after renal transplantation. In this communication we report the occurrence of peptic ulceration during the immediate post-transplantation period in a series of 500 kidney transplantations performed by our unit, and will discuss the possibility of preventing these serious complications.

Material and Methods

Five hundred kidney transplantations were performed between December 1964 and October 1976. There were 434 recipients, 107 transplants were obtained from living, related donors and 393 were cadaveric kidneys. The surgical techniques and immunosuppressive therapy used is reported elsewhere in this volume⁷. All patients were routinely treated before and after transplantation with oral aluminium hydroxide gel. Diagnosis of peptic ulceration
was based on clinical symptoms and signs and confirmed by upper G-I tract X-ray series, endoscopy and in case of death, by autopsy.

Results

Altogether 46 episodes of acute gastroduodenal ulceration were diagnosed in 45 patients, which gives an incidence of 9%. The mortality rate of this complication was high; 19 patients died (42%), the overall mortality for gastroduodenal ulceration being 3.8%. In 14 patients the peptic ulcer did not cause any complications, 25 patients bled, and in a further seven the ulcer perforated. Of the 25 bleeding episodes, 24 occurred during the immediate post-transplantation period and 12 episodes ended fatally, the mortality rate being 48%. Eleven bleeding episodes occurred during an acute rejection. In four patients the graft was removed after unsuccessful rejection treatment; none of these patients died. Of the remaining seven patients, where the graft was not removed, two died. In three cases upper gastrointestinal bleeding was associated with sepsis; all these patients died. Surgical treatment was attempted in three patients; in one patient partial gastrectomy with Billroth II reconstruction was performed but the patient died of anastomotic dehiscence. In two cases truncal vagotomy and pyloroplasty combined with oversewing the ulcer was done. One patient died two weeks later of rebleeding and one patient survived. In one patient highly selective vagotomy had been done earlier, but he bled again after transplantation in connection with an acute rejection. He was treated conservatively by gastric lavage with antacids. He remains well.

In seven patients perforation of gastroduodenal ulcer was observed and all these patients died. One of these patients had bled during her previous transplantation. In six cases the perforation occurred during treatment for acute rejection. Only two patients were operated upon (simple closure). In five the diagnosis was first established at autopsy.

Discussion

Gastroduodenal ulceration remains a major problem in clinical transplantation, as indicated by this and several previous reports. It is obvious that some means of effective prophylaxis is needed in order to reduce the incidence of the often lethal complications. Unfortunately, the cause of gastroduodenal ulceration is still unknown. However, there is general agreement that reduction of gastric acid secretion generally heals or prevents the occurrence of duodenal ulceration. At least some patients on regular haemodialysis have an increased acid secretion and it is known that these patients have an increased incidence of peptic ulceration. During the post-transplantation period several other factors contribute to an increased incidence of severe peptic ulceration. Steroid administration, especially during rejection therapy worsens the situation. Steroids do not increase gastric secretion, but they mask symptoms and signs causing delay in instituting the proper treatment, decrease the production of protective gastric mucus and above all negatively influence tissue repair. Other important factors in transplant patients
are renal malfunction and defects in the blood coagulation mechanisms. The thrombocytopenia frequently observed during rejection episodes makes bleeding difficult to control.

The obvious means to reduce gastroduodenal ulceration during the post-transplantation period would be effective prophylaxis, but the problem is how to effect this. Identification of the patients who will develop gastroduodenal ulceration is important. However, only about 50% of the patients who subsequently bled after renal transplantation had previous symptoms of gastroduodenal ulceration. This means that we should attempt to evaluate all transplantation candidates as regards their gastric secretion status combined with serum gastrin analysis and endoscopy.

There is no general agreement on the means to effect reduction of gastric acid output in transplantation patients. This should be done effectively and without untoward side effects. Prophylactic antacid therapy is not effective enough, as shown by our results and others. The value of anticholinergic drugs in preventing complications of duodenal ulceration is doubtful. As to the surgical procedures, there are several problems. Uraemic patients are often hypergastrinaemic. The rise in serum gastrin is directly proportional to the serum creatinine and returns to normal after renal transplantation. The operation that carries least side-effects is no doubt highly selective vagotomy, and would thus be a suitable form of prophylactic surgery for these patients, whose general condition is often poor. However, deaths have been reported from necrosis of the lesser curvature in uraemic patients when highly selective vagotomy was performed.

We had one patient on whom highly selective vagotomy was done previously; he bled after transplantation. Analysis showed that in this patient the operation had not reduced gastric acid secretion from the preoperative values. This was apparently due to the fact that the patient had very high values of serum gastrin, which remains unaffected by highly selective vagotomy. Spanos et al. used vagotomy and pyloroplasty as a prophylactic measure in some of their patients, but this could not prevent gastrointestinal bleeding after transplantation in 25% of cases. At least in those patients who are hypergastrinaemic hypersecretors, partial gastric resection combined with removal of as much proximal duodenum as possible, and reconstruction of the continuity of the gastrointestinal tract so that food bypasses the duodenum, seems preferable, as recommended by Gedde-Dahl and Flatmark. However, the relatively high operative mortality and late morbidity should be kept in mind.

The new drugs, $H_2$-blocking agents are, theoretically at least, very interesting in this connection. They do reduce acid secretion even in hypergastrinaemic subjects and cimetidine seems to be safe to use in uraemic patients.

We have recently treated successfully with cimetidine one patient who bled after vagotomy from his duodenal ulcer. This patient had a well-functioning kidney transplant. Prompted by the favourable reports on this drug we have started a study designed to evaluate whether cimetidine, used prophylactically, can help to resolve the serious problem of peptic ulceration in kidney transplant patients.
References

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Open Discussion

NIK-AKHTAR (Teheran) We have found that the incidence of peptic ulceration in 32 patients on chronic dialysis had an 8:1 male to female ratio. Peptic ulceration occurs more often in the second year of chronic dialysis than the first year. Is vagotomy still a justifiable prophylactic procedure in this group of patients?

DOHERTY I agree with you that vagotomy is not justifiable as a prophylactic procedure. The argument may be advanced that the mortality associated with vagotomy is less than 0.5%. This figure however relates to healthy patients, not to patients with terminal renal failure, in whom the mortality may be significantly higher. Furthermore, bleeding, when it does occur post-transplant is often not from the ulcer but in fact from gastric erosions, and vagotomy has not been shown to influence the development of these.

EKLUND Vagotomy is not sufficient in these patients.

GELIN (Gothenburg) Our statement in Gothenburg is that it might be justified in the ordinary patients but not in the uraemic patients. There is a different physiology behind it and the lesion is often multiple and therefore we prefer gastric resection.

MACSEARRAIGH (Durban) Dr Doherty has given adequate argument against
prophylactic surgery. The question I would like to ask is: because of the risk of steroid-induced ulceration and because of the stress factor of transplantation, does he believe that the routine use of cimetidine might in fact be appropriate for all dialysis patients, particularly those awaiting transplantation?

DOHERTY Could I say in answer to that, "Yes and No"? Yes, it has potentially wide application in dialysis patients, but No I do not think it is appropriate as a universal treatment. It is necessary to have a policy of gastric assessment; you must know whether the patient is a hypersecretor of acid or a hyposecretor of acid, as there is obviously no point in giving an acid-lowering drug to a patient who has no acid. The achlorhydric patient may still bleed on the basis of gastritis, but this is unlikely to be helped by cimetidine. There is perhaps some argument for the use of mucosa-protecting drugs such as colloidal bismuth preparations or carbenoxolone. So my answer is that it should not be given as a universal panacea, but gastric assessment will define which patients should in theory benefit from it.

R JONES (London) I would like to ask both of the previous speakers what is their experience of oesophagitis caused by candida. We are becoming increasingly aware of its incidence in patients with both acute and chronic renal failure and also following renal transplantation. Its significance varies from a cause of dyspepsia to a cause of fatal haemorrhage.

DOHERTY Only one of our five renal transplant patients who bled had oesophagitis as the cause of bleeding, and we had no evidence that this was a candida oesophagitis. It was probably oesophagitis related to acid reflux.

WATT (Preston) We seem to get conflicting reports in the literature on what happens when patients on cimetidine stop taking it. I wonder if Dr Doherty had any experience of having withdrawn the treatment or of patients who defaulted on the treatment; whether in fact this increased the acid secretion to higher than previous levels, and if so did you have any problems as a result?

DOHERTY That is something which I am looking at at present. I could not say that I have any conclusive evidence as yet, but it is a relevant concern, because cimetidine is basically a drug which interrupts a closed loop feedback system, and therefore has potential for causing rebound on stopping treatment.

WATT Have you seen any side effects of $H_2$ blockers in these patients?

DOHERTY No serious side effects have occurred to date in addition to the minor effects I listed on one of my slides. One further side effect we have seen has been mild breast enlargement and tenderness in a male patient.