PREVENTION OF UPPER GASTROINTESTINAL COMPLICATIONS AFTER KIDNEY TRANSPLANTATION

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Summary

In 94 renal transplant patients, the incidence and mortality rate of upper gastrointestinal complications was lower than in 11 other reports comprising over three thousand patients. This difference may be due to the smaller doses of prednisolone used. Duodenal ulcer and erosive gastritis were the commonest lesions and 73% occurred in the first 6 months after operation.

In 131 transplant candidates, gastric assessment including endoscopy showed 34 (26%) had peptic ulceration prior to operation. In 130 subjects (38 renal transplant, 68 chronic uraemia, 24 controls), pentagastrin tests showed acid hypersecretion in uraemic patients undergoing dialysis (P < 0.02) and a tendency for acid output to decrease after operation (P < 0.005). In 8 transplant patients with duodenal ulcer, preliminary experience with prophylactic cimetidine has been favourable.

Upper gastrointestinal complications after renal transplantation are likely to be lessened by, a) use of less prednisolone in the early post-transplant phase; b) pre-transplant gastric assessment and c) the use of a safe and effective antisecretory drug in those with duodenal ulcer.

Introduction

Many centres have reported a high incidence of upper gastrointestinal (UGI) bleeding and perforation in renal transplant (RT) recipients. The mortality of these complications is commonly over 50% [1] and they account for 7.5% of all deaths in these patients [2]. The aim of this study was to review the occurrence of UGI complications in patients transplanted at the Belfast City Hospital, and to compare it with experience elsewhere. In addition, the value of pre-transplant gastric assessment was examined, the effect of transplantation on gastric function was studied, and preliminary experience with cimetidine in transplant patients was reviewed.
Methods

Pre-transplant Gastric Assessment

Barium meal During the period 1968—77, all patients accepted for the dialysis and transplant programme of the Belfast City Hospital had a routine barium meal examination. Results were available for retrospective analysis in 131 patients.

Endoscopy Twenty-six of the 131 in addition had endoscopic assessment, usually because of X-ray negative bleeding/dyspepsia or equivocal X-ray appearances.

Tests of Gastric Acid Secretion

Peak acid output (PAO) was measured by standard pentagastrin test in 38 RT patients, 24 normal subjects, and 68 patients with advanced uraemia (of whom 36 were receiving regular dialysis therapy). Informed consent was obtained from all subjects. The Mann-Whitney 'U' test was used for analysis of this data. In the RT group, age, prednisolone dosage and time elapsed post-transplant were recorded; PAO was correlated with these variables using linear regression and partial coefficient analysis.

Management of Patients with Peptic Ulcer Prior to Transplantation

Thirteen of the 94 transplant patients had uncomplicated pyloroduodenal ulcer before transplantation, and the clinical course of their ulcer disease was recorded. Following transplantation, 5 of the 13 received antacids, 8 received cimetidine. Prophylactic cimetidine 400 mg daily (in divided doses) was given from the day of transplantation until creatinine clearance exceeded 20 ml/minute, when the dose was increased to 800 mg daily. This was reduced to 400 mg daily after 3 months and was stopped at 6 months. After 6 months, if a patient with known duodenal ulcer required antirejection therapy, cimetidine 800 mg daily was given until prednisolone dosage returned to maintenance level.

UGI Complications

Clinically overt episodes of UGI bleeding or perforation were recorded in 94 transplant patients, and compared with 11 similar reports [3–13]. These were scrutinised with regard to incidence and mortality rate of UGI complications, causative lesions and time of occurrence, and prednisolone dosage during the early post-transplant phase. Patients transplanted in Belfast receive 800 mg hydrocortisone on the first day, 20 mg prednisolone daily for 3 months, and thereafter are gradually reduced to 10 mg daily; regimes which considerably exceeded this dosage were designated 'high'. In Belfast, the steroid regime for antirejection is 200 mg prednisolone daily, reducing in five or three day steps to the maintenance level.
Results

Pre-transplant Gastric Assessment

Of the 131 patients who had barium meal examinations prior to transplantation, peptic ulceration was found in 17. A further 14 were diagnosed by endoscopic examination, and a further 3 had ulcer disease as an incidental finding at postmortem examination. Thus, a total of 34 patients (26%) had peptic ulceration (Table I).

TABLE I. Upper Gastrointestinal Tract Findings in 131 Transplant Candidates

<table>
<thead>
<tr>
<th>Finding</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>63</td>
</tr>
<tr>
<td>Peptic ulceration*</td>
<td>34 (26%)</td>
</tr>
<tr>
<td>Coarse gastric and/or duodenal mucosa</td>
<td>20</td>
</tr>
<tr>
<td>Hiatus hernia</td>
<td>5</td>
</tr>
<tr>
<td>Miscellaneous†</td>
<td>9</td>
</tr>
</tbody>
</table>

* Active DU                                   | 12                 |
* Chronic DU                                   | 16                 |
* Chronic prepyloric ulceration               | 4                  |
DU + GU                                       | 1                  |
GU                                            | 1                  |
† Delayed gastric emptying                    | 4                  |
† Increased resting juice                      | 2                  |
† Hypotonic duodenal loop                     | 1                  |
† Oedematous small bowel mucosa               | 1                  |
† Duodenal diverticulum                       | 1                  |

Gastric Acid Secretion

Peak acid output in RT patients and in patients undergoing regular dialysis was significantly higher compared with normal subjects, $P < 0.01$, $P < 0.02$ respectively (Figure 1). In the group of 38 RT patients (Figure 2), there was a significant negative correlation between PAO and time elapsed post-transplant ($r = -0.442$, $P < 0.005$); this remained significant ($P < 0.02$) after controlling for the influence of age by partial coefficient analysis. There was a weak positive correlation between PAO and prednisolone dosage ($r = 0.372$, $P < 0.02$), but this was not independent of time post-transplant or age.

Patients with Peptic Ulcer Prior to Transplantation

Of the 5 patients treated with antacids following transplantation, one patient died from UGI bleeding following antirejection treatment given at 22 months. Of the 8 patients treated with prophylactic cimetidine, one patient died from cerebral haemorrhage; none have experienced UGI complications, and none have had any major side effects attributable to cimetidine.

UGI Complications

Six of 94 RT patients developed UGI bleeding or perforation, and one of the 6 died. This incidence and mortality rate is compared with 11 other reports
Figure 1. Peak acid output in renal transplant (RT) patients, regular dialysis (RD) patients and patients with chronic uraemia (CRF) compared with normal subjects. (*P < 0.02; **P < 0.01)

Figure 2. Relationship of peak acid output and time elapsed post-transplant in 38 renal transplant patients
in Table II. In 10 of these 11 reports, information was supplied regarding causative lesions and their time of occurrence after operation; 164 patients (5%) of a total of 3,284 developed UGI complications (Table III); acute gastroduodenal ulcer and erosive gastritis were the commonest causes, and 73% occurred within the first 6 months after transplantation.

TABLE III. Causes of 164 Upper Gastrointestinal Complications Occurring in 3,284 Renal Transplant Patients (Eclectic data based on 10 reports)

<table>
<thead>
<tr>
<th>UGI lesion</th>
<th>Number of patients</th>
<th>Percentage of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal ulcer*</td>
<td>101</td>
<td>60%</td>
</tr>
<tr>
<td>Anastomotic ulcer</td>
<td>12</td>
<td>7%</td>
</tr>
<tr>
<td>Erosive gastritis</td>
<td>10</td>
<td>6%</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>10</td>
<td>6%</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>77</td>
<td>4%</td>
</tr>
<tr>
<td>Mallory-Weiss tear</td>
<td>1</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Not specified</td>
<td>23</td>
<td>16%</td>
</tr>
</tbody>
</table>

* includes pyloric ulcer; combined duodenal and gastric ulcer.
73% of these complications occurred in the first 6 months after transplantation.

Discussion

The study showed that the incidence of UGI complications in the Belfast series was lower than in most other reports, and that there was a striking contrast in mortality rates between the Belfast patients (17%) and patients
in the 11 other series (all higher than 40%). Unfortunately, not all of the series reviewed supplied information concerning immunosuppressive regimes; of those which did, all employed notably higher initial prednisolone dosage. These data are by no means conclusive, but they suggest that high dose prednisolone in the early post-transplant period is associated with an increase in frequency and mortality of UGI complications. The observation that 73% of such complications occur in the first six months also suggests a link with the high prednisolone dosage of the early post-transplant phase. Maintenance dosage of prednisolone varies little between different centres, the average dose being 10–20 mg daily. The great variation lies in the initial dosage regime, i.e. during the first four to eight weeks post-transplant, some centres employing exceedingly high levels (between 50 and 400 mg prednisolone) during this period. There have been no controlled trials comparing different prednisolone regimes, but a study of immunosuppression used in 16 centres undertaking kidney transplantation suggested that higher initial doses of prednisolone were no more beneficial and had obvious disadvantages [14]. Sparing use of steroid in the initial post-operative period, is therefore desirable as it may lessen UGI complications, and there is no evidence to suggest such regimes increase graft rejection. There is also a lack of clearcut evidence concerning the benefit of other immunosuppressive agents used for treatment of rejection episodes (actinomycin C, cyclophosphamide, antilymphocyte globulin), and a similar situation exists with regard to anticoagulants (heparin) and anti-platelet drugs (dipyridamole, cyproheptadine). All these drugs may contribute a bleeding tendency and thus increase the hazard of UGI haemorrhage occurring in association with acute rejection.

Table II shows that the majority of UGI complications after transplantation are caused by acute gastroduodenal ulcer and erosive gastritis. Acute gastroduodenal ulcers ('stress ulcers') are considered 'peptic' lesions, whereas erosive gastritis appears to be due to back diffusion of hydrogen ions caused by breakdown of the gastric mucosal barrier as a result of a variety of factors, e.g. alcohol, urea, salicylate [15].

Most clinical studies which do not employ routine endoscopy probably underestimate the incidence of erosive gastritis [16], and the figures given in Table III are undoubtedly too low, as six of the reports on which the figures are based excluded cases where UGI complications were due to this cause. When erosive gastritis occurs in the renal transplant patient, the clinical setting is often acute rejection, and therefore acute uraemia [17] and infection [18] may be implicated. The role of high dose steroid is unclear [19] but it is likely that it acts synergistically with other erosive influences. Renal transplant patients with stable graft function may develop erosive gastritis following ingestion of salicylate [20], and steroids increase the likelihood of this occurrence [19].

A crucial question is whether acute stress ulcer in the early post-transplant phase (or in association with acute rejection) is a de novo lesion or an acute exacerbation of a chronic peptic ulcer. Chisholm and associates [8] carried out a routine barium meal in uraemic patients and found an ulcer frequency similar to the normal population, and did not find this of help in predicting
the patients who would develop UGI complications after operation. They therefore concluded that UGI complications were new lesions induced by steroid therapy. However, we have found a high incidence of peptic ulcer in patients with chronic renal failure, perhaps because fibreoptic endoscopy was used as well as barium meal examination. The finding of gastric hypersecretion in patients undergoing regular dialysis (Figure 1) is further evidence that the ulcer disease antedates transplantation, and after operation the known effects of corticosteroids on gastric mucus [21] and tissue repair [22] could logically produce reactivation or complications of already existing ulcer disease. Conn and Blitzer in an extensive review of world literature [23] were able to document a significant association between peptic ulceration and steroid therapy only in patients who had received a cumulative dose in excess of 1000 mg prednisolone. The renal transplant patient obviously falls into this category, and some de novo ulcers may therefore occur due to the influence of corticosteroid therapy. However, the size of this effect is likely to be small (as judged from the figures given by Conn and Blitzer), and we conclude that most acute peptic ulcers in renal transplant patients are steroid-induced exacerbations of pre-existing disease. We feel that the most important aspect of pre-transplant gastric assessment is endoscopic examination of the UGI tract, as no further information is necessary if this reveals an ulcer crater. If, however, chronic ulcer scarring is found, either fundal biopsy or a pentagastrin test is desirable, as a few of these patients show the unusual association of atrophic gastritis and achlorhydria. Prophylactic acid-lowering measures are obviously illogical in this group. In contrast, some uraemic patients with duodenal ulcer have acid hyper-secretion associated with massive elevations in plasma gastrin, and there is some evidence to suggest that the clinical course of ulcer disease in such patients tends to be severe [25]. Measurements of acid secretion and plasma gastrin may therefore be helpful in assessing prognosis of ulcer disease in uraemic patients, but study of greater numbers of patients is necessary to clarify this point.

Prophylactic vagotomy has been advocated for all potential recipients [9], those with acid hypersecretion [26] or those with peptic ulcer [4]. There are, however, many arguments against prophylactic vagotomy [24], and the finding that acid secretion tends to decrease after transplantation (Figure 2) must add to these. The most plausible explanation for this trend in acid output is the associated change in circulating gastrin levels [27], as this hormone is known to exert a trophic effect on gastric mucosa [28].

It has recently been suggested that all patients should receive prophylactic cimetidine in the early post-operative phase [29]. However, this study has shown that pre-transplant gastric assessment will identify those patients likely to benefit from prophylactic cimetidine, and this seems preferable to employing a third drug on a ‘routine’ basis. Furthermore, clinical experience with cimetidine is still at an early stage, and some hazards may be as yet unidentified. In this study, preliminary results with cimetidine in 8 transplant patients with duodenal ulcer have been favourable, and there may also be a case for use of cimetidine in those with endoscopic evidence of duodenitis or oesophagitis prior to operation. Erosive gastritis is usually a self-limiting lesion,
seldom requiring surgery, and in addition, H₂-receptor antagonists are highly effective in the control of bleeding due to erosive gastritis [30]. It may therefore be argued that an expectant policy is justified.

On the basis of the present study, we recommend that assessment of the upper gastrointestinal tract should be included in screening renal transplant candidates. In those with uncomplicated peptic ulcer prophylactic vagotomy is unnecessary and cimetidine is a more logical alternative. In addition, the use of high dosage prednisolone in the early post-transplant period should be critically reappraised.

Acknowledgments

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References

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Open Discussion

GELIN (Chairman) I think all centres now experience lower incidence of the very severe gastrointestinal complications, and it happens to coincide with the appearance of the \( H_2 \) blockers.

FARR (Hull) Could I ask you how many patients were endoscoped, had radiological studies and acid secretion studies? How many of your patients had all those three investigations?

DOHERTY All 131 of the patients had a barium meal. Twenty-six of the 131 endoscopic investigation, and 68 patients before transplant had a pentagastrin test. Perhaps I should say that I do not advocate routine pentagastrin tests — they have little clinical value, and were carried out in this study essentially for research purposes. Our feeling is that the most important gastric investigation is endoscopic assessment. If this shows an active ulcer crater you do not need any further information. If you find chronic scarring and deformity, then a pentagastrin test is useful because occasionally the unusual association of atrophic gastritis may be found. So in those patients a pentagastrin test is useful in deciding if prophylactic treatment is necessary.

FARR I asked because we find that sometimes endoscopy is not as reliable as we might expect it to be, and radiology certainly isn’t.

JONES (London) I would just like to make one or two comments about the prophylactic use of cimetidine following transplantation. I agree that radiology is very difficult to interpret in uraemic patients for various reasons, and anyway a negative endoscopy or an abnormal acid study have been clearly shown to be poor predictors of the likelihood of haemorrhage or perforation following transplantation. The second reason why we feel that prophylactic cimetidine is worth giving is that the prevention of acute oesophageal, gastric and duodenal erosions is thereby achieved. Although I agree these are occasionally self-limiting, they may be very difficult to treat and are much less amenable to surgery than haemorrhage from a single ulcer.

DOHERTY Yes, I agree with you that we should try to prevent complications due to erosions as well as those due to duodenal ulcer. But I think the way to do this is to give less prednisone, not more cimetidine.

JONES I think we use a lot of steroid!

DOHERTY Yes. If you do get bleeding from acute mucosal erosions, it has been our experience and also that elsewhere, that this is very responsive to
treatment with \( H_2 \)-receptor blockers. But we feel low dose steroid and an expectant policy is the preferable alternative.

**BELL (Leicester)** I think you are quite right about treating duodenal ulcers that you find beforehand. The trouble is, of course, that there is a lot of evidence accumulating, albeit of an anecdotal nature, that stopping cimetidine, once it's started, is not as easy as it may seem. There is often a rebound in patients with DUs and we often see perforations which we had not expected. I wonder whether or not just giving cimetidine to these patients is the wrong thing to do for these reasons. Because you have the continuing stimulation by the steroids etc in the long term, and I would like to say that you shouldn't really bury vagotomy and pyloroplasty, and I still think that this should be used for patients with proven DUs for the reasons I have stated. Any comment on that?

**DOHERTY** Yes. Firstly, on your last comment, I think the risk of low doses of maintenance prednisolone — with regard to the upper gastrointestinal tract — is greatly overestimated. We have many patients with known duodenal ulcer disease who are taking 10–20 mg prednisolone without problems. The high risk period is in the early months post transplant and later with acute rejection episodes — temporary prophylactic treatment therefore seems more logical than permanent surgical measures. So I think that surgery should be reserved for complicated ulcer, or ulcer unresponsive to adequate medical treatment. I do not think it is justified for uncomplicated DU, if in addition you use prednisone sparingly, and give cimetidine prophylactically during times of high risk.

There is a lot of speculation about rebound on stopping treatment in the literature, but it is, as you say, based on anecdotal information, and not proven. I think policy on this issue should be based on factual information. Rebound hypergastrinaemia after stopping cimetidine has been recorded, but remembering the mechanism of feedback inhibition of gastrin release, this probably indicates that the parietal cell remains suppressed for some time after you stop treatment. No one has presented evidence of rebound hyperacidity yet. With regard to rebound in ulcer symptoms, it is very difficult to prove that such relapse after stopping cimetidine is not simply the natural course of the ulcer disease, as peptic ulcer is characterised by a course of remissions and relapses anyway. I think you will not see this sort of problem unless you give cimetidine for very long periods, and by that I mean more than a year, two years, three years.

**ZAZGORKI (Vienna)** We studied the gastrin blood levels after standard test meal after transplantation, and we could not find any difference between healthy controls and renal transplant patients. Do you do some prophylactic superselective vagotomy or something like that? There are reports that cimetidine could increase cellular response. Did you observe that the frequency of renal rejection is increased in the patients treated by cimetidine?

**DOHERTY** I am aware of the recent letter in the Lancet from Primack in America concerning children to whom he gave cimetidine, two of whom developed acute rejection at the same time as the commencement of cimetidine. Again this evidence is anecdotal. In our 8 patients we have not had any
evidence that it has enhanced graft rejection. With regard to your question about highly selective vagotomy — for an ulcer which has not responded to an adequate trial of medical therapy — highly selective vagotomy is the usual procedure carried out.

PARSONS (London) There is another hormone called parathyroid hormone which persists after transplantation for many years. I just wonder, do you have any evidence that the level of acid secretion after transplant is related to parathyroid hormone secretion? Have you done any PTH measurements at all?

DOHERTY We have looked at the possible relationship of parathyroid function in five patients, but this number is too small to draw any conclusions. I agree with you that it is another variable relevant to the observed trend in acid output post-transplant. I should say that parathormone does not have a trophic effect on the gastric mucosa and I think that gastrin is the more likely candidate to explain this phenomenon.

LINDSTRÖM (Helsinki) I agree with your conclusions in every respect. You mentioned our material on one of your slides, from Helsinki 1977. We reduced the dose of prednisolone in March 1975 and since then we have had much less complications with gastric bleeding and duodenal ulcers. We also used prophylactic cimetidine, but I can’t report any conclusions from that. We had one case where we had done partial gastrectomy before transplantation, but he started to bleed after transplantation. We did a vagotomy on him and he continued to bleed. After cimetidine he stopped. So there might be some indications for a combination of surgery (vagotomy) and cimetidine in some cases.

DOHERTY I think cimetidine may prove to be useful in bleeding from DU’s which is due to capillary ooze, if you like, from the ulcer bed. On the other hand, in cases where there is obvious and brisk arterial bleeding, there is little likelihood that cimetidine will be of benefit. I think that endoscopic assessment of the bleeding site will help decide whether or not to use cimetidine.