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Short-term high-dose corticosteroids and gastroduodenal mucosa

A prospective clinical study on renal transplant recipients

H. Paimela[1], K. Höckerstedt[2], H. von Numers[2], and J. Ahonen[2]

[1] Department of Surgery, Malmi Hospital, Sairaalakatu 3, SF-00700 Helsinki, Finland
[2] IV Department of Surgery, Helsinki University Central Hospital, Kasarmikatu 11–13, SF-00130 Helsinki 13, Finland

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Abstract. In order to evaluate the effect of a short-term high-dose corticosteroid therapy on the gastric and duodenal mucosa, 30 consecutive renal transplant recipients (mean age 39.1 years, 10 women and 20 men) underwent an endoscopic examination of gastroduodenal mucosa 12 and 30 days after renal transplantation. In addition to the postoperative immunosuppressive medication (methylprednisolone and azathioprine), antacids and H2-receptor antagonists were given. Seventeen patients showed no signs of acute rejection, whereas 11 patients experienced one episode and 2 patients two episodes of rejection during endoscopic follow-up. Each rejection episode was treated with a high-dose regimen of methylprednisolone. The two groups of patients studied, i.e., those who did and those who did not experience rejection, were matched for age, sex, period of preoperative dialysis treatment, period of postoperative time elapsed from transplantation, serum creatinine level, and dose of methylprednisolone or azathioprine at the beginning of the endoscopic follow-up, as well as for ulcer prophylactic medication during follow-up. The gastroduodenal mucosa was similar in the two patient groups, both endoscopically and histologically, at the start of the study. During the observation period of 2 weeks, erosive antral gastritis increased significantly in patients who did not experience rejection, whereas in patients with acute rejection and concomitant high-dose corticosteroid therapy, the antral mucosa remained nearly unchanged. Also, the gastric corpus and the duodenum remained unaltered in both groups during follow-up. No ulcer complications occurred in the series. Thus, a high-dose short-term corticosteroid treatment does not seem to be related to grossly harmful side effects in the gastroduodenal mucosa in the immediate post-transplant phase after renal transplantation. This suggests that the current policy of active treatment of renal failure, including antiulcer prophylaxis with H2-receptor antagonists and improved immunosuppressive medication, renders the gastroduodenal mucosa resistant enough to also tolerate the acute post-transplant period well.

Offprint requests to: K. Höckerstedt

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Even though the harmful effect of nonsteroidal anti-inflammatory drugs on gastroduodenal mucosa has been established, the effect of corticosteroids on this mucosal area is somewhat unclear [5–7]. There are experimental data on both favorable and unfavorable effects of corticosteroids on the gastroduodenal mucosa [3]. Also clinically the opinions on the subject are conflicting, even though the harmful gastrointestinal side effects of long-term therapy have repeatedly been documented [9, 15]. As for short-term high-dose treatment, the literature is meager.

The present study aims to evaluate the influence of a short-term high-dose corticosteroid treatment of the gastroduodenal mucosa in renal transplant recipients. This was done by comparing the endoscopic and histologic findings of the stomach and duodenum in renal transplant recipients experiencing no rejection with those of patients experiencing acute rejection episodes with concomitant high-dose corticosteroid therapy 12 and 30 days after transplantation.

Patients and methods

Patients

The series consisted of 30 consecutive cadaveric renal transplant recipients (mean age 39.1 years, range 17–56 years; 10 women and 20 men) with a primary kidney disease (Table 1). Seventeen patients showed no signs of acute rejection, 11 experienced one episode, and 2 patients two reversible rejection episodes, verified clinically and also by fine needle aspiration cytology of the kidney graft during the endoscopic follow-up. The patients were accepted for the study after informed consent, regardless of their history of acid-peptic disease, and all were normocalcemic.

Medication

In addition to the immunosuppressive medication, all patients were given antacids and histamine-H2-receptor antagonists. All medication except for the antacid was started on the day of surgery; the lat-

Table 1. Data on patients in the study

Variable	Patients experiencing rejection ($n = 13$)	Patients not experiencing rejection ($n = 17$)
Age (years)	42.4 ± 3.2	36.6 ± 2.9
Female/male ratio	6/7	4/13
Period of dialysis treatment before transplantation (months)	9.3 ± 2.9	9.3 ± 2.3
Renal disease		
- Glomerulonephritis	6	10
- Pyelonephritis	-	1
- Diabetic nephropathy	4	4
- Amyloidosis	-	1
- Other	3	1
Period from transplantation (days)		
- At first endoscopy	12.5 ± 1.0	12.6 ± 0.3
- At second endoscopy	35.5 ± 2.4	30.0 ± 1.3*
Serum creatinine (μmol/l)		
- At first endoscopy	544.5 ± 94.8	305.5 ± 84.5
- At second endoscopy	536.7 ± 98.4	148.2 ± 20.0*
Duration of acute tubular necrosis after transplantation (days)	15.3 ± 2.5	7.4 ± 1.9*
Hemodialysis patients after transplantation	3	-
Total dose of aluminum hydroxide (ml/kg)		
- At first endoscopy	17.6 ± 1.9	18.7 ± 1.3
- At second endoscopy	48.1 ± 4.1	45.4 ± 2.1

* $P < 0.05$; Student's t-test and Chi-squared test; mean ± SEM

ter was started on the 1st postoperative day. Coffee consumption and the use of nonsteroidal anti-inflammatory drugs were not allowed during the 1st postoperative month. H2-receptor antagonists (Zantac, Glaxo Group, Greenford, England; $n = 14$ or Tagamet, Lääke, Turku, Finland; $n = 16$) were used in all patients and the dose was adjusted according to serum creatinine levels. Aluminium-hydroxide antacid (Neutragel, Star, Tampere, Finland) was administered at a dose of 60–90 ml/day. The immunosuppressive treatment regimen consisted of a combination of azathioprine (Imurel, Wellcome, London, England) and methylprednisolone (Solu-Medrol/Medrol, Upjohn, Punis, Belgium) [11]. The dose of azathioprine at the start of administration was 2.0 mg/kg per day, and the subsequent dose changes were based on clinical variables. A maintenance dose of 2.0 mg/kg per day was targeted. The initial dose of methylprednisolone was 200–250 mg/day divided into three doses. It was stepwise tapered down by 40 mg daily within 4 days after the operation. After the 4th postoperative day, the drug was given as two divided doses. In case of acute rejection, the dose was increased to 3.0 mg/kg per day divided into four doses. In addition to the medical treatment, irradiation therapy on the transplant up to four times with 150 rad was also given to four patients as antirejection treatment.

Endoscopic analysis

All patients underwent two successive endoscopic examinations, whenever possible 12 and 30 days after transplantation. In patients who experienced rejection, the timing of the examination was adjusted according to the clinical course or the general condition of the patient. Endoscopy was performed by the authors (HP/HvN) with an Olympus-GIF-Q10 panendoscope; they were unaware of the possible occurrence of rejections.

The endoscopic findings were interpreted as follows (score): normal finding (0); increased redness of the mucosa, usually appearing as longitudinal stripes in the antrum, no erosions or ulcer (1); the above findings combined with one erosion (2); and two or more erosions and/or ulcer combined with the above findings (3).

Histologic analysis

Specimens for histologic analysis were taken at endoscopy only in patients with inflammatory findings and not routinely in order to speed up the examination and to avoid unnecessary complications in these patients with an increased tendency to bleed. Biopsy specimens were fixed in 10% formalin, cut to 5 μm thick sections, and stained with HE and Alcian blue (pH 2.5)-PAS. In histologic analysis performed by a pathologist who was unaware of the clinical course of the recipient, both acute and chronic mucosal lesions were assessed.

The acute histologic findings were interpreted as follows (score): normal histology (0), mild (1), moderate (2), or severe (3) erosive acute gastritis. The chronic changes were interpreted as follows (score): normal (0), mild (1), moderate (2), or severe (3) superficial gastritis, and mild (4), moderate (5), or severe (6) atrophic gastritis, as interpreted by the presence of chronic inflammation and loss of normal mucosal glands. In addition, attention was paid to the presence of intestinal metaplastic changes and dysplastic changes [18, 19].

Statistical analysis

The Student's t-test for unpaired observations, the Wilcoxon's rank sum test, the Chi-squared test, and the one-way analysis of variance were used in the statistical analysis.

All of the procedures in the present study were in accordance with the ethical standards of the Helsinki Declaration of 1975.

Results

The mean time of appearance of the first rejection episode was 17.50 ± 2.70 days post-transplant (mean ± SEM), thus occurring between the two endoscopic examinations in the rejecting patients. In four patients experiencing more than one rejection episode, the first endoscopic examination had already been preceded by a rejection episode and high-dose corticosteroid treatment.

Endoscopic findings

No ulcer complications occurred in the present series. The mean score of endoscopic findings on day 12 post-transplant was similar in the corpus, antrum, and duodenum in rejecting and nonrejecting patients. Even though an obvious tendency to worsening of the endoscopic findings could be observed in all of the above-named regions during follow-up, only in the nonrejecting patients did the mean score of endoscopic changes in the antrum worsen significantly ($P < 0.05$; Tables 2, 3). In the mild form, the findings were characterized by redness of the mucosa with red, longitudinal stripes entering the pyloric ring. In the moderate form, they were accompanied by an erosion. In the severe form, which was encountered in one nonrejecting patient, multiple erosions were accompanied by a prepyloric ulcer. No obvious reflux of duodenal contents into the stomach was observed in the series.

Table 2. Endoscopic findings of the gastroduodenal mucosa in patients experiencing and not experiencing rejection episodes on days 12 and 30 post-transplant after renal transplantation

Variable	Patients experiencing rejection ($n = 13$)		Patients not experiencing rejection ($n = 17$)	
	Day 12	Day 30	Day 12	Day 30
Stomach				
Body				
– Normal	12	9	15	11
– Mild inflammation	–	4	2	4
– Moderate inflammation	1	–	–	2
Antrum				
– Normal	7	5	11	4*
– Mild inflammation	5	4	6	9
– Moderate inflammation	1	4	–	3
– Severe inflammation	–	–	–	1
Duodenum				
– Normal	10	9	14	13
– Mild inflammation	3	3	2	4
– Moderate inflammation	–	1	1	–

* $P < 0.05$; Chi-squared test

Table 3. Mean score of endoscopic findings of the gastroduodenal mucosa in rejecting and nonrejecting patients on days 12 and 30 post-transplant

Variable	Day 12		Day 30	
	Rejecting ($n = 13$)	Nonrejecting ($n = 17$)	Rejecting ($n = 13$)	Nonrejecting ($n = 17$)
Corpus	0.15 ± 0.15 NS	0.12 ± 0.10	0.31 ± 0.13 NS	0.47 ± 0.18
Antrum	0.53 ± 0.18 NS	0.35 ± 0.12	0.92 ± 0.24 NS	1.05 ± 0.20*

* $P < 0.05$ between day 12 and day 30 in nonrejectors; one-way analysis of variance and Wilcoxon's rank sum test; mean ± SEM

Table 4. Mean score of acute histologic changes of gastric mucosa in rejecting and nonrejecting patients on days 12 and 30 post-transplant

Variable	Day 12		Day 30	
	Rejecting ($n = 2$)	Nonrejecting ($n = 6$)	Rejecting ($n = 4$)	Nonrejecting ($n = 7$)
Corpus	1.00 ± 0.00	0.33 ± 0.21	0.00 ± 0.00	0.42 ± 0.20
Antrum	2.50 ± 0.36	0.50 ± 0.32	0.60 ± 0.50	0.71 ± 0.46

NS for all; one-way analysis of variance and Wilcoxon's rank sum test; mean ± SEM

Histologic findings

The mean score of chronic gastritis in the corpus area was 0.45 ± 0.14 in nonrejecting and 0.17 ± 0.16 in rejecting patients (NS). There was a significant positive correlation between the endoscopic findings and the acute histologic changes of the gastric mucosa ($P < 0.001$). The mean score of acute histologic changes was also similar in rejecting and nonrejecting patients, both in the antrum and in the corpus at the start of the study (NS; Table 4). During follow-up, no significant change occurred in the acute histologic alterations of gastric mucosa in rejecting or nonrejecting patients. Dysplastic changes were encountered in one nonrejecting patient with a prepyloric ulcer.

Immunosuppressive medication

The mean total amount of methylprednisolone received by patients who did not experience rejection episodes was 2414.10 ± 132.60 mg during the study period of 30 days. The respective amount in patients who did experience rejection was 3602.70 ± 268.20 mg ($P < 0.001$). The mean total amount of azathioprine was 71.00 ± 4.80 mg/kg in rejecting patients and 60.00 ± 2.60 mg/kg in nonrejecting patients (NS).

Discussion

Opinions regarding the effect of corticosteroid therapy on the gastroduodenal mucosa are conflicting, and the ulcerogenic character of corticosteroids has not been unequivocally clinically documented [5–7, 15]. Corticosteroids are known to affect gastric mucosa by inhibiting the biosynthesis of prostaglandins, thereby inhibiting the gastric alkaline response and thus predisposing the epithelium to acid-peptic lesions [3, 8]. These drugs are also known to exacerbate subclinical intestinal infections, which may lead to perforative lesions in animals and in humans on corticosteroid medication [3]. On the other hand, in experimental studies, it has been shown that parenteral hydrocortisone does not cause any grossly harmful effect or microscopic injury to fundic mucosa in the hamster; the overall effect of this drug is the depression of epithelial renewal [14]. A favorable effect of corticosteroids on experimental gastrointestinal lesions induced by an intravenous platelet-activating factor has been documented by Wallace and Whittle [22]. They have shown in rats that corticosteroid pretreatment significantly reduces the severity of experimental gastrointestinal lesions in endotoxin shock. If an experimental gastric mucosal lesion is induced by histamine, corticosteroids are known to reduce the increased capillary permeability, thereby also reducing the severity of mucosal lesions [21]. Corticosteroids thus have both favorable and unfavorable effects on the upper gastrointestinal mucosa. The unfavorable effects are known to be mainly dependent upon the duration and dosage of corticosteroid therapy. The mode of administration, whether oral or parenteral, seems to be less important in this regard [20]. In renal transplant recipients, the deleterious effect of corticosteroids on epithelial renewal may be pronounced, due to the accompanying immunosuppressive therapy.

The aim of the present study was to evaluate the acute gastric mucosal changes during the immediate postoperative phase after renal transplantation. The background for the study was our previous report of gastroduodenal mucosal lesions in uremic and renal transplant recipients [17]. We observed that during long-term follow-up, gastroduodenal findings in uremic and renal transplant recipients are both endoscopically and histologically quite similar and comparable even to nonuremic controls. Thus, the increased incidence of upper gastrointestinal lesions reported among transplant recipients [1] is probably confined and detectable only during the acute postoperative phase and may be related to corticosteroid treatment.

Even though the increased incidence of upper gastrointestinal complications in renal transplant recipients has been repeatedly reported, no prospective endoscopic data on the subject thus far exists [1, 2, 4, 10, 13].

The present study showed that patients who did not experience any rejection episodes and who, at baseline, were on an antirejection regimen had more severe acute mucosal changes in the gastric antrum than patients with high-dose corticosteroid therapy as antirejection treatment. Compared to our previously reported series of patients on chronic hemodialysis treatment, the present findings were only slightly worse [17]. In nearly half of the patients histologic analysis was also available. It revealed that endoscopic assessment of acute mucosal damage is a reliable method in transplant patients as well and does not necessarily require a complementary histologic study, unlike chronic lesions, which can be detected only by histologic analysis. On the basis of the specimens available, the acute gastric erosive lesions are mostly mild and similar in rejecting and nonrejecting post-transplant patients. This observation is in accordance with the anti-inflammatory effect of corticosteroids in general. It is also in agreement with the findings of Jama et al. [12], in which corticosteroid therapy decreased the incidence of stress ulceration in various shock states. The similarity of chronic gastritic changes suggests that the groups were also comparable with regard to the acid secretion capacities of the stomach.

Thus, the present observation cannot be explained in terms of differing gastric acid secretion, something which is known to be decreased in these patients [16] and which was inhibited further with comparable doses of H2-receptor antagonists. The acute mucosal lesions encountered in these patients in the immediate post-transplant period probably have some pathogenetic mechanism other than the classic acid-peptic type injury. An important mechanism through which corticosteroids might affect the mucosal protection would be a decrease in the production of mucosal immunoglobulin A production, especially if this were accompanied by immunosuppressive therapy. This may render the mucosa vulnerable to microbial lesions, which are known to occur in these patients [2]. In the present series, no signs of severe acute viral infection were observed. Moreover, the antral epithelium and its mucus layer are often subjected to duodenogastric reflux, which may, in combination with corticosteroids, impair the buffering properties of the mucus layer. In this study no obvious duodenogastric reflux was, however, observed.

We may conclude that acute gastroduodenal mucosal lesions, as assessed by endoscopy with histology, are mild during the 1st postoperative month after renal transplantation, even though the number of acute lesions in the antrum tend to increase. The endoscopic changes of the antral mucosa are, however, less severe in patients on high-dose corticosteroid antirejection therapy than in patients who do not experience any rejection episodes, suggesting that high-dose corticosteroid therapy does not induce any grossly harmful gastroduodenal side effects in the immediate post-transplant period. The modern principles of antiulcer prophylactic measures in renal transplant surgery, including H2-receptor antagonists and improved immunosuppressive medication, seem to provide an efficient means of preventing upper gastrointestinal complications, also in the immediate post-transplant phase.

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