Transpl Int (1997) 10: 375–378

ORIGINAL ARTICLE

I. Skála
O. Marečková
Š. Vítko
I. Matl
J. Lácha

Prophylaxis of acute gastroduodenal bleeding after renal transplantation

Received: 24 February 1997
Received after revision: 15 April 1997
Accepted: 17 April 1997

I. Skála (✉) · O. Marečková
Š. Vítko · I. Matl · J. Lácha
Institute for Clinical and
Experimental Medicine, Vídeňská 800,
CZ-140 00 Prague 4, Czech Republic
Fax: + 4 20 24 72 22 55

Abstract Severe gastroduodenal bleeding after renal transplantation is effectively prevented by H_2 receptor blockers. New drugs for prophylaxis include proton pump inhibitors. The aim of the present study was to compare the effects of prophylaxis with the H_2 blocker ranitidine and with the proton pump inhibitor omeprazole. One hundred seventy-seven consecutive patients were included in a controlled, prospective, randomized study after cadaveric renal transplantation. In one case, ranitidine failed to prevent exsanguination due to duodenal peptic ulcer bleeding. No bleeding was noted in the omeprazole group. There were no significant differences between the groups in hospitalization time, development of renal function, amount of cyclosporin A, prednisone, azathioprine, or methylprednisolone ingested, or laboratory biochemical parameters. We conclude that prophylaxis of severe gastroduodenal bleeding after renal transplantation with omeprazole is effective. Omeprazole is certainly as good as ranitidine; its advantages are a prolonged effect and a simple dosage, independent of graft function development.

Key words GI bleeding, H_2 receptor blockers, kidney transplantation · H_2 receptor blockers, GI bleeding, kidney transplantation · Kidney transplantation, GI bleeding, H_2 receptor blockers

Introduction

Acute gastroduodenal bleeding and/or peptic gastroduodenal lesions are well-known complications after renal transplantation (RTx) and, when they occur, they are associated with significant morbidity and mortality rates. Recent improvements in medical care and prevention with histamine-H_2 receptor antagonists have helped reduce this danger [2, 3, 6, 7, 9]. The introduction of proton pump inhibitors into clinical practice expands the arsenal of pharmacological prophylaxis.

When administering prophylaxis with H_2 blockers, it is necessary to reduce the dose according to the degree of renal function development. Omeprazole, the first and best-known proton pump inhibitor, has a powerful and long-lasting inhibitory effect on gastric acid secretion, and there is no need to adjust the dose to the decrease in renal graft function. These properties of omeprazole are likely to be advantageous in prophylaxis for renal transplant recipients.

The aim of this study was to compare the efficacy of prophylactic administration of omeprazole with that of the H_2 blocker ranitidine to establish whether or not omeprazole is safe after RTx.

Materials and methods

In a prospective, controlled, randomized study, 177 consecutive recipients of cadaveric kidney transplants were prophylactically treated with either ranitidine (Ranital injection, Lek, Slovenia; Ranisan tablets, Pro Med CS, Czech Republic) or omeprazole (Losec;

Table 1 Characteristics of patients after transplantation

Treatment	Omeprazole		Ranitidine	
	n	Age (years)	*n*	Age (years)
Men	45	44.2 (20–67)	50	45.2 (19–65)
Women	39	49.6 (28–64)	43	43.0 (19–70)
Total	84	46.2 (20–67)	93	44.5 (19–70)

Astra, Sweden). The characteristics of the groups of patients are given in Table 1 and their dosing schedules in Table 2. In the ranitidine group, a history of peptic gastroduodenal lesions and/or gastroduodenal bleeding was found in seven patients, and stomach resection was noted in one patient. In the group of patients treated with omeprazole, a positive history of peptic ulcers was confirmed in four patients and three patients had undergone preventive surgery. After RTx, the patients were put on conventional immunosuppression, i.e., prednisone 30 mg/day, azathioprine 1.5 mg/kg b.w. per day, and cyclosporin A 5 mg/kg b.w. per day. Serum cyclosporin A levels were determined twice a week. Therapeutic levels were kept between 300 and 600 ng/ml. The serum levels of cyclosporin A were assessed with the RIA method with polyspecific monoclonal antibody. The dosage of oral cyclosporin A was adjusted twice a week to maintain this range. The diagnosis of rejection was established on the basis of graft biopsy. Rejection episodes were treated with methylprednisolone, OKT 3, and/or ATG (ALG). Statistics were evaluated with Student's *t*-test and the χ^2 test.

Results

Neither ranitidine nor omeprazole administration was associated with any clinically significant side effects (even when administered intravenously) requiring drug withdrawal. No significant differences in the onset and development of graft function were seen (Fig. 1), not even at the level of function after a stabilized state was achieved. No significant differences were found in the amount of cyclosporin A, prednisone, azathioprine, or methylprednisolone ingested, or in laboratory parameters (blood count, sedimentation rate, aminotransferases, bilirubin, alkaline phosphatase). Differences in hospitalization time between the groups were negligible (Fig. 2). The incidence of rejection episodes diagnosed by graft biopsy did not differ between the ranitidine- and omeprazole-treated groups.

The amount of methylprednisolone and cyclosporin A ingested (Fig. 3) was identical in both groups. If cyclosporin A metabolism were to change due to interaction with omeprazole, then the serum levels of cyclosporin A and, consequently, the intake of oral cyclosporin A would also be affected. Thus, intake of cyclosporin A should serve as an indicator of changes in the metabolism of this drug.

One of our patients died due to bleeding from a duodenal ulcer. This patient was in the ranitidine group. He was a 48-year-old man with a history of ulcers, and he had been bleeding 2 years prior to RTx. Graft function started to develop quickly after RTx although, on day 2 post-RTx, the patient had surgical revision for a urinary fistula. On post-RTx day 5, he was found to have melena, and gastroduodenoscopy proved multiple bleeding duodenal ulcerous lesions. Conservative treatment was unsuccessful and the patient died on day 14 after RTx. Autopsy revealed ulcerophlegmonous esophagitis with perforation into the mediastinum and the thoracic cavity. Bilateral hemothorax with pulmonary collapse and freshly dispersed catarrhal bronchopneumonia were found. The cause of death was exsanguination from duodenal ulcers.

Discussion

In the past, gastroduodenal bleeding was a relatively frequent complication after organ transplantation. Factors that play a role in its development include gastric hyperacidity and damage to the protective mucosal barrier, especially stress, and perhaps also immunosuppressive therapy. The importance of bleeding has been documented in numerous studies [2, 3, 6, 7, 9]. Very representative data have been provided by Blohme [3]. In his group of 468 transplant patients, bleeding developed in 10.2 %, and 3.6 % patients died of it. An analogous picture is provided by a group of kidney recipients at our Institute in the period before pharmacological prophylaxis (1966–1978). Bleeding occurred in 9.5 % of 190

Table 2 Dosing scheme. Randomization was according to even/odd years of birth (*SCr* concentration of serum creatinine, *tbl* tablet, *inj* injection)

	Ranitidine tbl 150 mg inj. 50 mg Even years of birth	Omeprazole tbl 20 mg inj. 40 mg Odd years of birth
Day 0	1 ampule i.v.	1 ampule i.v.
Days 1–3	1 ampule i.v. twice daily	1 ampule i.v.
Day 4 to end of hospitalization	SCr > 300 μmol/l 1 tbl evening SCr < 300 μmol/l 1 tbl twice a day + antacid[a] 10 ml six times a day	1 tbl morning
Hemodialysis	1 tbl morning + 1 tbl pre- and posthemodialysis + antacid 10 ml six times a day	1 tbl after hemodialysis

[a] Anacid: Algeldrati suspensio quantum aequivalens aluminii trioxidi 250 mg, magnesii hydroxidum 250 mg, in 5-ml suspension (Galena, Czech Republic)

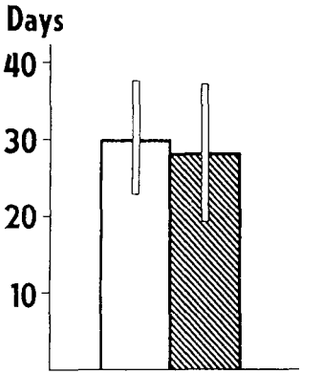

Fig. 1 Mean hospitalization time in both groups ± SD. The difference is statistically non-significant. □ Omeprazole; ▨ ranitidine

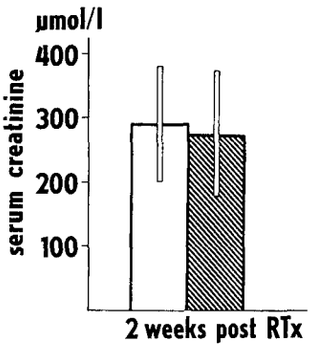

Fig. 2 Development of function of the renal graft, evaluated by serum creatinine levels at 2 weeks after transplantation. Mean values ± SD are shown. The difference is statistically non-significant. □ Omeprazole; ▨ ranitidine

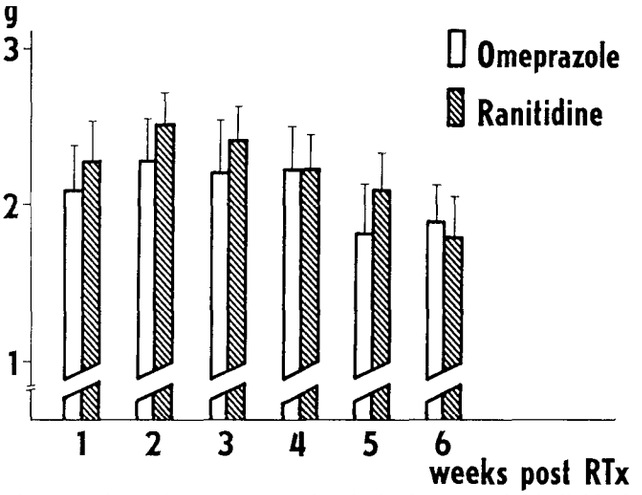

Fig. 3 Cyclosporin A consumption in both groups by individual weeks after renal transplantation. Mean values ± SD are shown. The differences are statistically non-significant

kidney recipients, and 3.6 % died of and bleeding-related causes.

The incidence of complications of the upper gastrointestinal tract following RTx has declined in recent years because of pre-transplant screening and post-transplant prophylaxis with H_2 antagonists. Needless to say, factors playing a role in this trend are the current immunosuppressive therapy with a reduced corticoid dosage and the better overall care provided for patients undergoing RTx. In our clinic, we improved the unfavorable situation in 1978, when we introduced a series of prophylactic measures consisting of gastroenterological examination of RTx candidates (i.e., history, barium meal examination and/or endoscopy), surgical prevention (gastric resection, proximal selective vagotomy) in patients at an increased risk of bleeding, and systematic use of pharmacological prevention with cimetidine or ranitidine with antacids after RTx. The long-term experience we have gained confirms the benefits of prophylaxis: there have been almost no deaths from gastroduodenal bleeding in the early post-RTx period and, when bleeding has occured, it has always been mild and controlled by conservative therapy.

Progress over the past decade has considerably improved the potential for prophylaxis and treatment of peptic gastroduodenal lesions. A new generation of H_2 blockers that are more effective and have fewer side effects, and, recently, inhibitors of the proton pump of parietal cells of the gastric mucosa, have been introduced into clinical practice. These facts made us revise the series of prophylactic measures we are currently using.

Even the new generation of more effective H_2 receptor blockers is not completely devoid of undesirable side effects. Especially the interactions with the metabolism of a number of drugs in the liver (cytochrome P 450) are important. Prophylaxis with H_2 receptor blockers is made difficult by the need to adjust the dosage to the reduction in renal function. Inhibitors of the proton pump of parietal cells of the gastric mucosa are a major contribution. Omeprazole, the most widely used representative of this group of drugs, has been shown to be useful in the treatment of peptic lesions and reflux esophagitis. Its antisecretory action is potent, long-term (one dose daily is enough), and confined exclusively to parietal gastric cells. In general, omeprazole-associated adverse effects are mild and self-limiting, similar to those seen with histamine H_2-receptor antagonists and unrelated to dosage or patient age [10].

Intravenous administration of omeprazole is considered by some not to be completely free of risks on account of reports of visual and hearing impairment [8]. In our experience, the side effects of omeprazole, as described by our patients, were clinically negligible even when the drug had been administered i.v. No cases of impaired sight and hearing were observed. It is clear to-

day that these side effects are unlikely; however, our study could not exclude the possibility of omeprazole-related effects in rare cases. This problem could be avoided by using omeprazole in infusion or by using ranitidine for a very short period of 1 or 2 days after RTx when drugs are administered intravenously. Omeprazole does not affect liver function, heart activity, or blood pressure. As a result, there are no known contraindications to its administration. For prophylactic use of omeprazole in practice, it is important to know that one daily dose is enough, and there is no need to change the dose depending on graft function.

The efficacy and safety profile of omeprazole in the prophylaxis of ulcers and ulcer bleeding after RTx have not yet been established. Our study shows that prophylaxis with omeprazole is highly effective and fully comparable with ranitidine-based prophylaxis. At the same time, both drugs have considerably cut down the incidence of, or eliminated altogether, severe gastroduodenal bleeding. They are very well tolerated. The case of duodenal ulcer bleeding we reported is an exception rather than the rule.

It is very difficult to evaluate objectively the development and treatment of rejection episodes after RTx. In clinical practice, treatment of a rejection episode is commonly initiated with the administration of methylprednisolone in a bolus dose. As a result, methylprednisolone intake can be regarded as an indicator of the severity of rejection and duration of treatment of the rejection episode. The groups compared did not differ even in this parameter, suggesting that omeprazole has no significant effect on rejection activity.

It is known that omeprazole effects the metabolism of a number of drugs (warfarin, phenytoin, diazepam, antipyrine) by the cytochrome P 450 in the liver [5]. The question then arises as to whether the metabolism of cyclosporin A is also not affected. Arranz et al. [1] stressed that caution is advised with the concomitant administration of omeprazole and cyclosporin A. If the metabolism of cyclosporin A is hindered by omeprazole administration, the implication might be that a lower dose should be enough to reach therapeutic levels of omeprazole. Blohme et al. [4] monitored the changes in the serum levels of cyclosporin A in ten patients and found that omeprazole did not interfere significantly with cyclosporin A metabolism in stabilized renal transplant patients and, consequently, that it can be used without extra monitoring of blood cyclosporin A concentrations.

Our study extends this concept to a substantially larger group of patients, even in an unstable period of developing graft function post-RTx. The fact that there is no difference between ranitidine and omeprazole in terms of how they affect cyclosporin A metabolism is documented by unchanged cyclosporin A consumption when serum levels are kept within the therapeutic range. Our results thus show that omeprazole has no effect on cyclosporin A consumption.

Acknowledgements This study was supported by the Czech Grant Agency grant No. 947–3, and approved by the respective Ethics Review Board; therefore, it complies with the ethical standards formulated by the 1964 Declaration of Helsinki.

References

1. Arranz R, Yanez E, Franceschi JL, Fernandez-Ranada JM (1993) More about omeprazole-cyclosporine interaction. Am J Gastroenterol 88: 154–155
2. Benoît G, Moukarzel M, Verdelli G, Hiesse C, Buffet C, Bensadoun H, Charpentier B, Jardin A, Fries D (1993) Gastrointestinal complications in renal transplantation. Transpl Int 6: 45–49
3. Blohme I (1975) Gastro-duodenal bleeding after renal transplantation. Scand J Nephrol 29: 21–23
4. Blohme I, Idstrom JP, Andersson T (1993) A study of the interaction between omeprazole and cyclosporine in renal transplant patients. Br J Clin Pharmacol 35: 156–160
5. Creutzfeldt W (1994) Risk-benefit assessment of omeprazole in the treatment of gastrointestinal disorders. Drug Saf 10: 66–82
6. EDTA (1979) Combined report on intermittent dialysis and renal transplantation in Europe. XVIth Congress of the European Dialysis and Transplant Association, Amsterdam. In: BHB Robinson, JB Hawkins, RB Naik (eds). Pitman Medical, Bath, pp 31–40
7. Hájková B, Erben J, Fixa P, Herout V, Zahradník J, Kabelác K (1992) Gastrointestinal tract bleeding as the cause of death in patients after renal transplantation (in Czech, abstract in English). Vnitř Lék 38: 56–59
8. Labenz J, Stolze M (1995) Seh- und Horstorungen unter Omeprazole: Die Fakten. Leber Magen Darm 25: 6–8
9. Skála I, Kočandrle V, Vaněk I, Marečková O, Bláha J, Jirka J, Pirk F (1981) Prophylaxis of gastroduodenal complications using highly selective vagotomy and cimetidine with antacids in patients with chronic renal failure and in renal transplant recipients (in Czech, abstract in English). Rozhl Chir 60: 305–312
10. Wilde MI, McTavish D (1994) Omeprazole. An update of its pharmacology and therapeutic use in acid-related disorders. Drugs 48: 91–132