TITLE: Proton Pump Inhibitors (PPIs) in Renal Transplant Patients: Evidence for PPI of Choice

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CONTEXT AND POLICY ISSUES:

Gastrointestinal (GI) complications including gastroduodenal ulceration and GI bleeding can occur in up to 20% of renal transplant recipients and are responsible for substantial morbidity and mortality in this population. These adverse events may be the result of transplantation surgery, progression of disease, comorbidities, or the use of immunosuppressant drugs. The immunosuppressant drug mycophenolate mofetil (MMF) in particular is associated with a high incidence of GI adverse effects including diarrhea, abdominal pain, ulceration and GI bleeding. However, attempting to ameliorate GI symptoms by a reduction in dose or discontinuation of therapy has been associated with increased risk for acute rejection and poorer long-term graft survival. Therefore, early recognition and appropriate management of complications including prophylaxis against the development of ulcers and GI bleeding with proton pump inhibitors (PPIs) has been used to help reduce morbidity and mortality in renal transplant recipients.

There are currently five different PPIs on the Canadian market including omeprazole (Losec®), rabeprazole (Pariet®), lansoprazole (Prevacid®), pantoprazole (Panto® IV, Pantoloc®), and esomeprazole (Nexium®). Most comparative studies to date have demonstrated similar clinical effectiveness and safety among the different PPIs for various indications. PPIs (with the exception for rabeprazole) are extensively metabolized via the cytochrome P450 enzymes CYP2C19 and CYP3A4 in the liver. The potential for drug interactions is thought to be the greatest with omeprazole and esomeprazole. Although rabeprazole is partly metabolized by CYP2C19 and CYP3A4, the major metabolic pathway is non-enzymatic. Therefore, it is thought that rabeprazole may exhibit a lower risk for pharmacological interactions and be less susceptible to inter-individual genetic variations in CYP2C19 and CYP3A4.
Cyclosporine, tacrolimus, and MMF are immunosuppressive agents commonly prescribed in combination regimens to prevent acute rejection and loss of the renal allograft. Because PPIs, tacrolimus, and cyclosporine all use the CYP3A4 enzyme for hepatic elimination, increasing blood levels of these immunosuppressant drugs may occur when used concurrently. An increase in immunosuppressant blood levels beyond therapeutic range could potentially result in serious adverse effects including nephrotoxicity and neurotoxicity with cyclosporine and tacrolimus, or leucopenia and GI adverse effects with MMF. MMF metabolism to the active metabolite mycophenolic acid (MPA) is independent of the cytochrome P450 system making it less susceptible to interactions with drugs metabolized by these enzymes. However, interactions that decrease absorption of MPA into the bloodstream may still occur.

An assessment of the clinical effectiveness of various PPIs for treating GI complications as well as the potential for clinically relevant interactions with immunosuppressive drugs is necessary to help guide PPI selection in this population. This report will review the available evidence for the use of different PPIs in renal transplants patients.

**RESEARCH QUESTION:**

Is there any evidence that one proton pump inhibitor is best to use in renal transplant patients with gastrointestinal complications?

**METHODS:**

A limited literature search was conducted on key health technology assessment resources including OVID MEDLINE, OVID EMBASE, PubMed, the Cochrane Library (Issue 3, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results are limited to English language publications. No filters were applied to limit the retrieval by study type or date. This search was supplemented by hand searching the bibliographies of selected papers.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews and meta-analyses are presented first. These are followed by economic evaluations, randomized controlled trials, observational studies and evidence-based guidelines.

**SUMMARY OF FINDINGS:**

Two randomized controlled trials and six observational studies examining the use of PPIs in renal transplant patients were identified. Results of these studies are summarized in Table 1. No health technology assessments, systematic reviews, or guidelines were identified.

**Health technology assessments**

No literature identified.

**Systematic reviews and meta-analyses**

No literature identified.
**Randomized controlled trials**

**Lansoprazole and Rabeprazole**

Miura et al. examined the effect of rabeprazole and lansoprazole on blood levels of tacrolimus in renal transplant recipients with variations in the CYP2C19, CYP3A5, and MDR1 genes. Variations in CYP2C19, CYP3A5 (a CYP3A4 related enzyme with similar catalytic specificity), and MDR1 (a multidrug resistance gene) all may lead to increased levels of tacrolimus in the blood. Seventy-three living-donor recipients were randomly assigned after renal transplantation to receive repeated doses of tacrolimus for 28 days with either rabeprazole 20 mg/day (n=33) or lansoprazole 30 mg/day (n=40). All patients also received immunosuppressive therapy with MMF and steroids. After 28 days, the authors noted that all patients who had elevated tacrolimus blood levels when co-administered with rabeprazole or lansoprazole expressed a genetic variation in CYP3A5 (CYP3A5 *3/*3). Some, but not all, of these patients also expressed genetic variations in CYP2C19 (CYP2C19 *1/*2 and CYP2C19 *1/*3) and MDR1 (MDR13435CC+CT genotype). The degree of interaction between tacrolimus and rabeprazole was similar to that between tacrolimus and lansoprazole. The authors concluded that for renal transplant recipients with certain genetic variations, rabeprazole and lansoprazole may inhibit the metabolism of tacrolimus and lower dosages should be given. Limitations of this study include small sample size, short duration, and an absence of adverse event reporting.

**Omeprazole**

Blohme et al. conducted a randomized, blinded, cross-over trial examining the effect of omeprazole on renal transplant patients concurrently receiving treatment with cyclosporine. Ten male patients with stable kidney function (1-7 years post-transplant) were given omeprazole 20 mg/day (n=5) or placebo (n=5) for two consecutive weeks each. Blood samples for cyclosporine were taken in the morning (trough concentration) during a 2 week run in period before initiation of omeprazole, during the four week study period, and during a two week follow-up period. Results showed no clinically or statistically significant difference between trough concentration levels of cyclosporine with either treatment during the two month study period. No adverse effects were reported during administration of omeprazole. The authors concluded that omeprazole does not significantly interfere with cyclosporine metabolism in stabilized renal transplant patients. This study is limited by a small sample size and short duration.

**Observational studies**

**Lansoprazole and Rabeprazole**

Miura et al. investigated the effect of anti-ulcer prophylaxis with lansoprazole or rabeprazole on patients receiving MMF. Sixty-one living donor renal transplant recipients receiving immunosuppressive therapy with MMF, tacrolimus, and corticosteroids were retrospectively divided into patients that received lansoprazole 30 mg/day (n=22) or rabeprazole 10 mg/day (n=17), or patients that had withdrawal of PPI at 6 months after transplantation who were used as the no PPI control group(n=22). All patients had no previous history of gastric ulcer disease. One year after transplantation, plasma concentrations of MPA were significantly lower for those receiving lansoprazole than those being treated with rabeprazole (p<0.05) or not receiving a PPI (p<0.05). Genetic analysis for variations in CYP2C19 and MDR1 was carried out. In recipients with specific genetic variations in CYP2C19 (CYP2C19 *1/*2 or CYP2C19 *1/*3 genotype) or MDR1 (C3435T CC genotype), MPA plasma concentrations were significantly lower in those receiving lansoprazole than those being treated with rabeprazole (p<0.05) or not receiving a PPI.
These findings indicate that the administration of lansoprazole in patients with certain genetic variations may potentially diminish the absorption of MPA and increase the risk for acute rejection. However, the plasma concentration of MPA did not appear to be influenced by rabeprazole indicating this may be a safer option to use in this population. This study is limited by a small sample size, retrospective design, and a lack of reporting for adverse effects and graft rejection.

Itagaki et al. present two cases of the differing effects of lansoprazole and rabeprazole on blood levels of tacrolimus in renal transplant recipients with CYP2C19 gene mutations. In the first, a 57 year old woman underwent cadaveric renal transplantation and received tacrolimus, prednisolone, and MMF for immunosuppression. Lansoprazole 30 mg/day was started on post-operative day 19 due to the development of a peptic ulcer. Tacrolimus trough levels drastically increased 3 days after introducing lansoprazole. The authors did not note if any adverse effects occurred during the period tacrolimus blood levels were elevated. Switching lansoprazole to famotidine 40 mg/day on day 71 resulted in a decline in tacrolimus levels. On day 152, rabeprazole 10 mg/day was started to heal symptoms from the recurrence of a peptic ulcer. Levels of tacrolimus remained controlled in the therapeutic range with rabeprazole therapy. The concentration-to-dose (C/D) ratio was significantly increased for tacrolimus with lansoprazole treatment when compared with famotidine and rabeprazole (p<0.05 and P<0.01, respectively). The C/D ratios did not differ significantly between rabeprazole and famotidine. Genetic analysis revealed that this patient expressed a genetic mutation in the CYP2C19 gene (CYP2C19 *1/*2).

The second case was a 46 year old woman who underwent cadaveric renal transplantation. She received tacrolimus, prednisolone, and MMF as immunosuppressive agents. At two months after transplantation, she developed a duodenal ulcer and initiated therapy with famotidine 40 mg/day. No drug interactions were noted and beginning a year and a half after transplantation, rabeprazole 10 mg/day was initiated for the recurrence of a duodenal ulcer. The C/D ratios did not differ significantly between rabeprazole and famotidine, suggesting that rabeprazole did not impede the metabolism of tacrolimus. Genetic analysis revealed that the patient expressed a genetic mutation in the CYP2C19 gene (CYP2C19 *2/*3). The findings presented in these two case reports indicate that rabeprazole is a safer option to use in renal transplant recipients even when genetic variations for metabolizing enzymes are present.

**Lansoprazole**

Takahashi et al. describe a case of a significant interaction between lansoprazole and tacrolimus in a 34 year old Japanese man who received a living donor kidney transplant. The patient also received MMF and prednisolone for immunosuppression. Lansoprazole 30 mg/day was administered from postoperative day 4 as prophylaxis for ulcers. The trough concentration of tacrolimus increased markedly after the introduction of lansoprazole and remained high for 13 consecutive days. No serious adverse events were observed as a result of high blood concentrations of tacrolimus. Lansoprazole was discontinued on day 15 and replaced with famotidine 40 mg/day on day 17. The trough concentrations of tacrolimus returned to therapeutic range and were maintained at follow-up on post-operative day 28. Genetic analysis revealed a genetic variation in the CYP2C19 gene (CYP2C19 *1/*2).

**Omeprazole and Rabeprazole**

Takahashi et al. present a case report of a drug interaction between intravenous omeprazole and tacrolimus in a 32 year old Japanese male patient. After receiving a living-donor kidney transplant, the patient received tacrolimus, MMF, and prednisolone for immunosuppression. When the patient was switched on post-operative day 18 from oral ranitidine 150 mg/day to
intravenous omeprazole 40 mg/day to treat peptic ulcers, the trough level of tacrolimus markedly increased. Although the dosage of tacrolimus was gradually decreased, the trough level of tacrolimus remained above therapeutic range. However, no serious adverse events were observed as a result of the high blood concentration of tacrolimus. Omeprazole was replaced with oral rabeprazole 10 mg/day on post-operative day 21 and blood concentrations of tacrolimus returned to therapeutic range. The authors were unable to access genetic information, therefore it was not clear whether this patient expressed any genetic variations. The authors concluded that the case indicates that rabeprazole can safely be used in place of omeprazole in renal transplant patients receiving tacrolimus.

**Pantoprazole**

Lorf et al. investigated the effect of ulcer prophylaxis with pantoprazole 40 mg/day in six renal transplant patients receiving cyclosporine. All patients also received immunosuppressive therapy with prednisolone and three were treated with MMF. Results showed that pantoprazole did not affect cyclosporine trough levels during an observation period of up to 3 months. A second study conducted by the same authors assessed blood levels of both tacrolimus and cyclosporine in 12 transplant patients (7 kidney transplant, 3 heart transplant, and two liver transplant) receiving pantoprazole 40 mg/day given as prophylaxis for ulcer disease. Results showed that five consecutive days of therapy with pantoprazole did not significantly affect the trough levels of either tacrolimus or cyclosporine.

**Table 1: Summary of evidence for interactions between immunosuppressive drugs and PPIs in renal transplant recipients**

<table>
<thead>
<tr>
<th>Concurrent Immunosuppressant Drug</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>Unknown</td>
<td>Unknown</td>
<td>None&lt;sup&gt;14&lt;/sup&gt;</td>
<td>None&lt;sup&gt;18,19&lt;/sup&gt;</td>
<td>None</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Unknown</td>
<td>Increased blood concentrations of tacrolimus with CYP2C19 and CYP3A5 genetic variations&lt;sup&gt;13,16,17&lt;/sup&gt;</td>
<td>Increased blood concentrations of tacrolimus&lt;sup&gt;4&lt;/sup&gt; (genetic variations unknown)</td>
<td>None&lt;sup&gt;19&lt;/sup&gt;</td>
<td>None&lt;sup&gt;4,16&lt;/sup&gt;</td>
</tr>
<tr>
<td>MMF</td>
<td>Unknown</td>
<td>Decreased plasma concentrations of MPA with CYP2C19 or MDR1 genetic variations&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Unknown</td>
<td>None&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

MMF=Mycophenolate mofetil, MPA=Mycophenolic acid, MDR=multidrug resistance

**Guidelines**

No guidelines were identified that specifically addressed the use of PPIs for the treatment of GI complications in renal transplant recipients.
Limitations

Evidence for the use of PPIs in renal transplant recipients is limited to two small RCTs of short duration and various observational studies and case reports. Only a few of these studies reported adverse effects during the study period making it difficult to judge the clinical significance of possible interactions. None of these studies assessed the comparative clinical effectiveness of PPIs for preventing or resolving GI complications in renal transplant patients. As a result of this paucity of evidence, no guidelines have yet been developed indicating choice of PPIs for renal transplant recipients.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

In summary, evidence for the use of various PPIs in renal transplant patients is extremely limited. Poor quality evidence from case studies suggests that perhaps rabeprazole or pantoprazole may be the safest options for renal transplant patients receiving immunosuppressive therapy. However, despite a theoretically lower risk of drug interactions with rabeprazole, results are conflicting. Furthermore, the clinical significance of pharmacokinetic interactions reported with omeprazole and lansoprazole has not been evaluated adequately in clinical trials. The few studies that reported adverse events indicated that no adverse events were noted when blood levels of tacrolimus were increased beyond therapeutic values. No studies have been conducted using esomeprazole although currently available data indicate that this compound seems to have a propensity for drug interactions comparable to omeprazole. An absence of head-to-head comparative trials comparing different PPIs for clinically significant outcomes (e.g., incidence of hospitalization and mortality due to GI complications) makes it difficult to assess therapeutic superiority in renal transplant recipients. Current evidence indicates that genetic variations in the CYP2C19, CYP3A5, and MDR1 genes may increase the risk for PPI drug interactions with tacrolimus. However, it has not been established which genes produce clinically significant drug interactions in renal transplant patients. Since genetic information is not always available for each patient, further information is required to guide monitoring requirements for specific immunosuppressant drugs in order to optimize dosage regimens in renal transplant patients receiving PPIs. Until further evidence is available, the decision as to which PPI to select for the management of GI complications in renal transplant patients should take clinical experience and institution-specific costs into consideration.

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