Clinical Nephrology, Vol. 68 – No. 2/2007 (65-72)

ISSN 0301-0430

Proton pump inhibitors and the kidney: critical review

U.C. Brewster and M.A. Perazella

Section of Nephrology, Yale University School of Medicine, New Haven, CTt, USA

Key words
proton pump inhibitors – acute interstitial nephritis – acute kidney injury – chronic kidney disease – hyponatremia

Part of this work was presented at the ASN Annual Meeting in San Diego, 2006 (Clinical Nephrology Conference presentation)

Received
February 1, 2007;
accepted in revised form
March 12, 2007

Correspondence to
M.A. Perazella, MD, FACP
Associate Professor of Medicine, Director, Nephrology Fellowship Program, Section of Nephrology,
Yale University School of Medicine,
FMP 107, 330 Cedar Street, New Haven,
CT 06520-8029, USA
mark.perazella@yale.edu

Abstract. Proton pump inhibitors (PPIs) are widely prescribed to treat a number of gastrointestinal disorders due to excessive acid production. While effective and safe, adverse renal effects have been described. Most concerning is the ever increasing number of cases of acute interstitial nephritis (AIN) associated with PPI therapy. It appears to be a class effect as all PPIs have been documented to cause AIN. Several adverse drug event registries now note PPIs as the most common cause of drug-induced AIN. While most patients recover kidney function, many are left with some level of chronic kidney disease. Hyponatremia is an extremely rare complication and is thought to result from inappropriate ADH secretion. Interactions with calcineurin inhibitors may occur with certain PPIs when used in susceptible patients, particularly those with polymorphisms in the cytochrome P450-2C19 enzyme gene. This paper will critically review the effect of PPIs on the kidney.

Introduction

Proton pump inhibitors (PPIs) were first available in 1989 with the development of omeprazole, and since then, have become one of the most widely prescribed class of drugs currently on the market. Over 43 million prescriptions were written for anti-ulcer therapy in the United States (US) in 2005 [Brewster and Perazella 2007]. This compares with the 70 million prescriptions of NSAIDs and 30 billion over-the-counter doses of drug sold annually in the United States in 2001 [Green 2001]. There are five PPIs available in the US including omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. Their efficacy in treating acid-related disease processes is unmatched and their safety profile is excellent. This combination of effects is the primary reason why over 8 billion dollars in sales were noted in 2005; a considerable volume given that omeprazole has been available over the counter since 2003 [Brewster and Perazella 2007]. However, renal complications do exist. Reported events include acute interstitial nephritis (AIN), rare cases of hyponatremia and the potential for drug-drug interactions.

Pharmacology

Pharmacokinetics

Oral bioavailability of PPIs ranges from 30 – 90% [Physicians Desk Reference 2007]. All are highly protein bound and maintain a small volume of distribution (0.17 – 0.45 l/kg). Proton pump inhibitors are metabolized via the cytochrome P450 (CYP450) system, although important differences are evident as shown in Table 1 [Physicians Desk Reference 2007]. CYP450-2C19 and CYP450-3A4 are the primary enzyme systems involved in their metabolism. Lansoprazole is metabolized equally by both enzymes, but metabolism of esomeprazole, pantoprazole and omeprazole is predominately by CYP450-2C19 [Physicians Desk Reference 2007]. Rabeprazole is metabolized by the same cytochrome enzymes, but also undergoes non-enzymatic metabolism, circumventing the CYP450 pathways and allowing continued metabolism despite the presence of agents that compete for the CYP450 enzymes [Physicians Desk Reference 2007]. These subtleties have important implications for drug-drug interactions. Medications that are metabolized by these enzyme systems compete and may promote excessive drug levels and their associated toxicity.

Table 1. Proton pump inhibitor characteristics.

	Lansoprazole	Pantoprazole	Rabeprazole	Omeprazole	Esomeprazole
Dosage (mg/day)	15 – 30	40	20	20 – 40	20 – 40
Volume of distribution	0.39 l/kg	0.17 l/kg	N/A	0.34 – 0.37 l/kg	0.24 l/kg
Protein binding	97 – 99%	98%	95 – 98%	96%	97%
Bioavailability	15 mg = 81% 30 mg = 91%	77%	52%	30 – 40%	90%
Metabolism by CYP450 enzymes in the liver	CYP2C19 = CYP3A4	CYP2C19 > CYP3A4	CYP2C19 = CYP3A4 and nonenzymatic	CYP2C19 > CYP3A4	CYP2C19 > CYP3A4
Drug excretion	14 – 25% renal inactive metabolites, <1% parent drug in urine 67% bile	71 – 82% renal inactive metabolites, no active drug in urine 18 – 20% fecal	90% renal inactive metabolites, no active drug in urine 10% fecal	77% renal inactive metabolites, "minimal" parent drug in urine 19% bile	80% renal inactive metabolites, < 1% parent drug in urine

Abbreviations: N/A, data not available.

Inactive drug metabolites formed by the CYP450 enzymes are excreted by the kidneys, with 0 – 1% of active drug recoverable in the urine [Physicians Desk Reference 2007]. This pharmacokinetic profile allows drug therapy with no requirement for dosage adjustments in the setting of kidney failure. The PPIs, due to their extensive protein binding are not removed by hemodialysis; however, they do require dosage adjustment (decreased dose) in patients with severe liver disease.

Pharmacodynamics

Proton pump inhibitors reduce gastrointestinal acid production by inhibiting the H^+/K^+ ATPase present on the secretory surface of gastric parietal epithelial cells. Low gastric pH protonates the PPI, which converts it to its active form allowing covalent receptor binding and non-competitive inhibition of the pump [Howden and Reid 1984]. Both basal and stimulated acid secretion declines following this interaction. The active form of these drugs is metabolized by the liver into various inactive metabolites (hydroxy, desmethyl, sulfone molecules), which are subsequently excreted by the kidneys [Physicians Desk Reference 2007]. Importantly, although H^+/K^+ ATPase is present on distal renal tubular cells (intercalated cells), inactive metabolites have no in vivo effect on the pump, and seemingly no effect on urinary pH or K^+ excretion. In support of this, omeprazole administration to healthy male subjects did not alter electrolyte balance or urinary pH [Howden and Reid 1984].

Pharmacogenetics

Polymorphisms of the CYP450 enzyme genes are well described and modify the metabolism of many drugs, including the PPIs. This can disturb the expected drug dose/drug level relationship and subsequently elevate in vivo drug concentrations when other drugs that utilize these enzyme systems for metabolism are concurrently prescribed. Polymorphisms occur in Exon 4 or 5 of the CYP450-2C19 enzyme gene in 16 – 25% of Caucasians, 36 – 47% of Asians and 10% of African-Americans [Ishizaki and Horai 1999]. When these mutations exist, patients are classified as "poor metabolizers" and the area under the curve (AUC) of the administered drug is generally twice that of "normal metabolizers".

Acute interstitial nephritis

In general, AIN is a relatively uncommon cause of acute kidney injury (AKI), account-

ing for only 2 – 3% of all renal biopsies [Buysen et al. 1990, Davison and Jones 1998, Clarkson et al. 2004]. However, in patients with AKI and normal appearing kidneys on ultrasound, AIN is a much more common cause, accounting for up to 27% of biopsy-proven cases [Farrington et al. 1989]. Acute interstitial nephritis associated with PPIs, in this case omeprazole, was first published in 1992 [Ruffenach et al. 1992]. In this case, a 74-year-old female on omeprazole for 6 months, developed fatigue, malaise and was noted to have hematuria, proteinuria and eosinophiluria. Over the next 12 years, 29 cases with omeprazole were published, 23 of which were biopsy-proven [Geetha 1999, Geevasinga et al. 2005, Myers et al. 2001, Portera-Cailliau 1999, Post and Zanen 2000, Ra and Tobe 2004, Torregrosa et al. 2004, Wall et al. 2000]. In 2004, other PPIs (lansoprazole and pantoprazole) were implicated in two large case series [Simpson et al. 2006, Torpey et al. 2004].

In one of the earlier case series, all AIN cases diagnosed at Norwich University Hospital (UK) were collected over a 4-year period (1995 – 1999) [Torpey et al. 2004]. Of the 24 cases identified, 14 were drug-related, 8 of which (57%) were due to the PPIs omeprazole (n = 6) and lansoprazole (n = 2). Patients with AIN presented with AKI and non-specific symptoms. Although all recovered kidney function, many were left with some degree of chronic kidney disease (75%). A subsequent large case series from Auckland, New Zealand published in 2006 described 15 cases (12 biopsy-proven) of AIN associated with PPI therapy [Simpson et al. 2006]. Time from initiation of drug to development of clinical symptoms ranged from 10 days to 18 months. 12 out of 14 patients (86%) were left with chronic kidney disease (CKD) after recovery from AKI. These same authors also examined data from the Center for Adverse Reactions Monitoring (CARM) in New Zealand. They found that PPIs were the most common cause of drug-induced AIN in their region (32%), with an incidence of 1 : 12,500 patient-years [Simpson et al. 2006].

The largest report to date was published by investigators from Australia [Geevasinga et al. 2006]. Retrospective data collection from two teaching hospitals over a period of 10 years (1993 – 2003) forms the basis of the study. Cases were identified and demographics, clinical parameters and histopathology were examined in detail. 28 cases of biopsy-proven AIN were identified, 18 (64%) of which were associated with a PPI (omeprazole n = 11, pantoprazole n = 3, esomeprazole n = 3, rabeprazole n = 1). Mean time to development of AIN was 11 weeks after drug initiation. Classic histopathologic changes of AIN with cellular interstitial infiltrates and eosinophils were present in 83% of renal biopsy specimens. The authors also queried the Therapeutic Goods Administration (TGA) database, a governmental organization that records adverse drug events, for data reported from 1991 – 2004. After extensive review, cases were classified as either "biopsy-proven AIN", "suspected interstitial nephritis", "unexplained acute renal failure", and "renal impairment". 34 additional cases of "biopsy-proven AIN", 10 cases of "suspected interstitial nephritis", 20 cases of "unexplained renal failure" and 26 cases of "renal impairment" that were associated with PPIs were identified. These data do not prove cause and effect, but raise concern for a high frequency of association of AIN with PPI therapy.

Most recently, additional cases of AIN were reported from the Netherlands (omeprazole, pantoprazole, rabeprazole) [Harmark et al. 2007]. 5 out of 7 cases were biopsy-proven and all patients manifested symptom improvement following drug withdrawal. The authors subsequently queried the World Health Organization (WHO) Collaborating Center for International Drug Monitoring Database, which includes information on adverse drug reactions (ADR) from over 3.5 million reports. Another 150 cases of AIN attributed to PPIs were identified as reported to the registry by practicing clinicians. Although the rate appears low in this database study, the low numbers may be partially explained by the lack of awareness of PPI-induced AIN, relying on spontaneous physician reporting. Nonetheless, taken together, it appears that PPIs are the leading cause of drug-induced AIN.

Clinical presentation

Acute interstitial nephritis that develops following methicillin exposure presents clini-

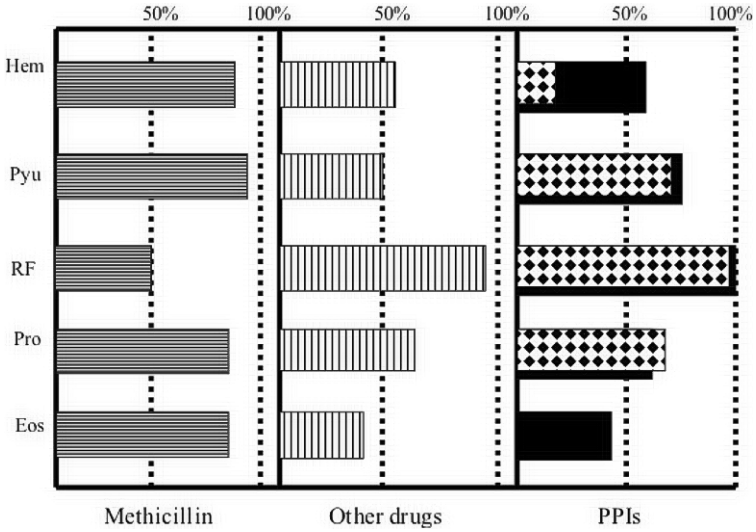

Figure 1. Clinical features of methicillin-induced AIN (longitudinal bars), non-methicillin drug-induced AIN (excluding NSAIDs) and PPI-induced AIN (Geevasinga et al. [2006] data, patterned bars; other PPI cases combined). Abbreviations: PPI: proton pump inhibitor; NSAIDs: nonsteroidal anti-inflammatory drugs (from [Brewster and Perazella 2007]).

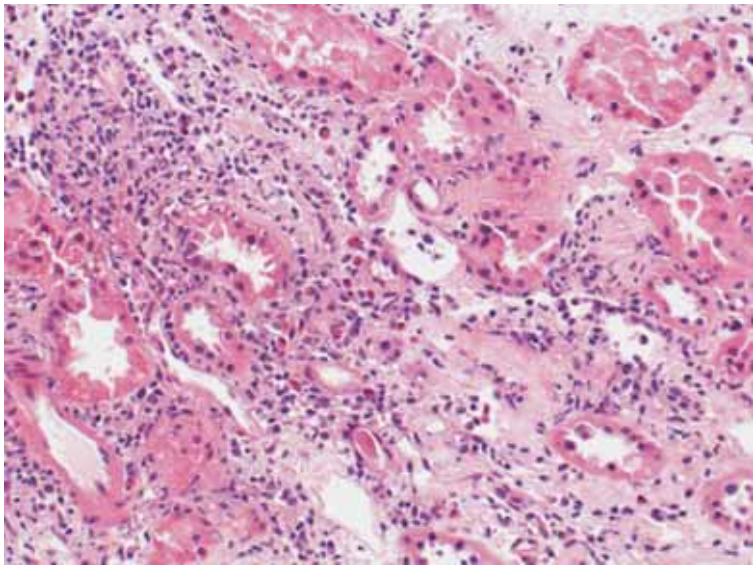

Figure 2. Kidney biopsy demonstrates a diffuse cellular infiltrate within the interstitium with inflammatory cells including eosinophils and lymphocytes. Tubulitis is present. Hematoxylin and eosin stain (from Brewster and Perazella [2007]).

cally as a hypersensitivity reaction, which is characterized by the triad of fever, rash and eosinophilia. In contrast, as with other non-methicillin type drugs, PPI-induced AIN does not manifest as a systemic "allergic reaction". Although data are not available in all cases, only about 10% of patients had the classic triad of hypersensitivity, less then half had fever, fewer then 10% had rash, and approximately 33% had eosinophilia. Non-specific complaints including weakness, fatigue, malaise and anorexia were common on presentation. Geevasinga et al. [2006] noted fatigue and nausea in 39% and weakness in 22% of patients. The clinical and laboratory findings that occur with AIN associated with methicillin, other non-methicillin type drugs (excluding NSAIDs), and PPI-induced AIN (all cases combined) are shown in Figure 1 [Brewster and Perazella 2007]. It is worth noting that the clinical and laboratory presentation of PPI-induced AIN is quite similar to that described with the non-methicillin type drugs.

The time interval from drug initiation to onset of clinical abnormalities (primarily kidney disease) is quite variable, occurring anywhere from 1 week to 9 months. Combining all published cases reveals that symptoms and/or identification of AIN developed on average 9.9 weeks after starting treatment with the PPI. This timing is actually quite similar to the time frame (11 weeks) described in the largest published series [Geevasinga et al. 2006]. Accidental or unrecognized drug rechallenge after suspected AIN from a PPI was associated with rapid onset of symptoms, with acute kidney injury developing within days of exposure [Assouad et al. 1994, Christensen et al. 1993, Gronich et al. 1994, Ruffenach et al. 1992].

Diagnosis and management

In general, a firm diagnosis of AIN from a PPI requires a renal biopsy given the infrequency with which classic signs and symptoms (systemic hypersensitivity reaction) occur. Urinalysis may reveal pyuria and hematuria, while urine sediment examination will sometimes demonstrate white blood cells (rarely eosinophils), red blood cells, and white blood cell casts; but they are inconsistent findings. Moreover, their absence may be misleading and hamper the diagnosis of PPI-induced AIN. Histopathology of renal tissue typically demonstrates an interstitial cellular infiltrate with or without tubulitis (Figure 2). The largest case series to date where biopsy findings were recorded documented eosinophils within the tubulointerstitium of 88% of

patients [Geevasinga et al. 2006]. In most cases, the glomeruli and vasculature were normal, unless another unrelated kidney lesion was also present.

Management of AIN associated with PPIs is similar to that of other forms of drug-induced AIN. Withdrawal of the offending agent remains the mainstay of therapy. In addition to drug cessation, the majority of cases of PPI-induced AIN underwent therapy with corticosteroids. Steroid therapy of AIN remains an active subject of debate and continues to be plagued by the absence of prospective randomized controlled trials. In the largest study to date, the course of 2,598 patients, of which 2.6% (n = 67) had AIN, was retrospectively evaluated [Clarkson et al. 2004]. No statistical difference was noted in the final serum creatinine concentration in patients treated with steroids as compared with those who did not receive the anti-inflammatory drug. Despite these data, uncontrolled data support the potential role of steroids in hastening renal recovery, albeit to a similar level of renal function, as compared with no therapy [Buysen et al. 1990, Pusey et al. 1983]. When treatment with steroids is employed, oral prednisone at 1 mg/kg/day for 1 – 2 months with a rapid taper is one possible regimen. Occasionally, high dose pulse intravenous steroids are used. Recently, mycophenylate mofetil (MMF) has shown promise as a treatment of both drug-induced and non-drug-associated AIN that were otherwise resistant or dependent on steroid therapy [Preddie et al. 2006]. Although, MMF represents a potential therapeutic option for patients with drug-induced AIN that is failing or dependent on steroids, better studies are required to more completely assess the role of anti-inflammatory therapy in treatment of drug-induced AIN.

Prognosis

Early diagnosis of PPI-induced AIN, as with all forms of drug-associated AIN, improves the long-term prognosis. Overtime, irreversible interstitial fibrosis may develop and ultimately promote CKD from chronic interstitial nephritis. In all the case reports published on PPI-induced AIN, very few patients required renal replacement therapy for AKI, and none developed end-stage renal disease requiring chronic maintenance dialysis. Importantly though, many patients were left with some level of renal impairment and CKD. In the study by Geevasinga et al. [2006], all patients recovered from AKI, however, they did not return to baseline kidney function. In fact, mean calculated creatinine clearance was 15.9 ml/min and 11.5 ml/min lower than baseline at 3 and 6 months, respectively, as most patients were left with stages 3 and 4 CKD. Similarly, Simpson et al. [2006] noted incomplete recovery of renal function after PPI-induced AIN. In this study, mean serum creatinine concentration increased from a baseline value of 0.94 mg/dl and settled at 1.57 mg/dl after 3 – 18 months. When one excludes data from Geevasinga and Simpson, other published cases confirm development of CKD as patients recovered to lower levels of kidney function (serum creatinine concentration 1.3 mg/dl) as compared with baseline (serum creatinine concentration 1.1 mg/dl) in those with AIN associated with PPI therapy.

Hyponatremia

Hyponatremia is a rare complication of PPI therapy [Castot et al. 1993, Durst et al. 1994, Gonthier et al. 1993, Kaloustian and Veyssier 1992, Melville et al. 1994, Mennecier et al. 2005, Shiba et al. 1996]. Currently, only 9 cases have been reported in the literature (Table 2). 8 of 9 cases describe omeprazole as the causative agent, while one case is attributed to esomeprazole. Serum sodium concentrations ranged from 108 – 124 mmol/l and in most cases, patients were symptomatic (headache, confusion). The association, however, is difficult to prove, as 3 of those cases had other possible causes of hyponatremia (volume depletion, concurrent illness) [Castot et al. 1993].

The pathophysiologic mechanism of hyponatremia is unclear, but seems most likely related to inappropriate antidiuretic hormone (ADH) production. Where it was documented, 4 of the 6 cases described a clinical scenario consistent with syndrome of inappropriate antidiuretic hormone (SIADH). In one case, a 66-year-old woman became profoundly symptomatic with a serum sodium concentra-

Table 2. Cases of hyponatremia attributed to proton pump inhibitors.

Case	Age/sex	Drug & Duration	Serum Na^+ (mEq/l)	Recovery time	Treatment	Cause
Kaloustian et al. 1992	70 M	Omeprazole 40 mg x 4 days	118	5 days	Water restrict and sodium supplement	SIADH
Gonthier et al. 1993	84 F	Omeprazole 40 mg x 11 days	106	8 days	Tetracycline	SIADH
Melville et al. 1994	5 M	Omeprazole 2 mg/kg x 10 days	122	1 day	Sodium supplement	Renal Na^+ wasting?
Durst et al. 1994	66 F	Omeprazole 40 mg x 5 months	124, 122	N/A	Sodium supplement	SIADH
Shiba et al. 1996	68 M	Omeprazole 20 mg x 4 days	111	7 days	Sodium supplement	Renal Na^+ wasting?
Mennecier et al. 2005	81 F	Esomeprazole 20 mg x 5 days	122	2 days	Water restriction	SIADH

Abbreviations: SIADH = syndrome of inappropriate antidiuretic hormone; Na^+ = sodium.

tion of 124 mmol/l, euvolemia on exam, and other laboratory data supporting SIADH [Durst et al. 1994]. Discontinuation of omeprazole and fluid restriction corrected underlying hyponatremia. Rechallenge with omeprazole induced recurrence of hyponatremia (serum sodium concentration 122 mmol/l). Again, drug discontinuation and water restriction normalized the serum sodium concentration. In two other cases, renal salt wasting was raised as a possible cause, although the data are far from definitive [Melville et al. 1994, Shiba et al. 1996]. In the first case [Melville et al. 1994], omeprazole therapy in a child with Klippel-Feil syndrome was associated with the development of hyponatremia and hypokalemia (with high urinary sodium and potassium concentrations). Cessation of omeprazole reduced the urinary sodium to concentrations appropriate to sodium intake and volume status. Taken together, the association of PPIs and hyponatremia is rare, but should be kept in mind when evaluating the hyponatremic patient who is receiving a PPI.

Implications for transplantation: drug interactions

Calcineurin inhibitors (CI) are staples of immunotherapy in renal transplant recipients. Because calcineurin inhibitors are metabolized primarily by the P450-CYP3A4 enzyme system, drug interactions may occur with PPIs that are metabolized predominantly by this pathway. Specifically, transplant patients utilizing this enzyme for PPI metabolism, may develop much higher calcineurin inhibitor drug level : drug dose ratios, suggesting impaired CI metabolism. In vitro studies have shown that omeprazole inhibits tacrolimus metabolism by liver microsomes by as much as 15% [Christians et al. 1996]. Several studies have examined dose level : drug dose ratios and found no effect on the ratios when concurrent PPI and CI therapy is undertaken. The first of these studied 12 transplant patients on either pantoprazole and tacrolimus (n = 6) or pantoprazole and cyclosporine (n = 6) and found no effect on trough CI levels with either drug combination [Lorf et al. 2000]. In this study, all patients were Caucasian (less likely to have CYP450 gene polymorphisms) and none underwent formal gene polymorphism testing. Subsequently, 51 transplant recipients on tacrolimus who were placed on omeprazole for 3 months were evaluated [Pascual et al. 2005]. Again, no change in drug levels was noted, but gene polymorphisms were not tested for in the study population.

As most PPIs rely predominantly on the CYP450-2C19 pathway for metabolism, it is understandable that studies, which include patients unlikely to have a polymorphism in

this gene will not manifest drug interactions or toxicity. However, mutations in the CYP-450-2C19 pathway make patients "poor metabolizers" of PPIs, shifting metabolism to the CYP450-3A4 enzyme. Studies that include renal transplant patients with this mutation demonstrate higher CI drug level : drug dose ratios. Case reports of patients with CYP450-2C19 mutations, who therefore rely more heavily on CYP450-3A4 enzyme, note higher drug level : drug dose ratios of tacrolimus when treated concurrently with lansoprazole [Itagaki et al. 2002]. This drug interaction does not occur, however, in patients administered rabeprazole as this agent has non-enzymatic pathways for metabolism. Despite this potential, drug interactions have not been described as a significant adverse effect of the PPIs.

Conclusion

Proton pump inhibitors are widely employed as therapy for acid-related gastrointestinal diseases. Their pharmacology is such that they do not require modification of drug dose or interval in patients with kidney disease, but do in those with significant hepatic disease. The PPI drug class is clearly associated with the development of AIN, with a clinical presentation similar to non-methicillin type drugs. As such, AIN from PPIs should be suspected as a potential cause of AKI in patients without an obvious cause of kidney dysfunction. In the majority of cases, recovery from AKI occurs following drug withdrawal (± steroids), however, most patients are left with some level of CKD. Hyponatremia occurs very rarely, likely the result of drug-induced SIADH. Proton pump inhibitors may interact with calcineurin inhibitors in organ transplant patients who possess mutations in the CYP450-2C19 enzyme system gene, although this has not been noted as a significant problem.

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