# Potential Adverse Drug Events and Nephrotoxicity Related to Prophylaxis With Omeprazole for Digestive Disorders: A Prospective Cohort Study

Fabiana Rossi Varallo, PhD[1,2]; Tales Rubens de Nadai, PhD[1,3]; Alice Rosa Alves de Oliveira[2]; and Patricia de Carvalho Mastroianni, PhD[2]

*[1]Americo Brasiliense State Hospital, Americo Brasiliense, São Paulo, Brazil; [2]São Paulo State University (UNESP), School of Pharmaceutical Sciences, Araraquara, São Paulo, Brazil; and [3]Department of Surgery and Anatomy, Ribeirão Preto School of Medicine, University of São Paulo, São Paulo, Brazil*

## ABSTRACT

**Purpose:** The purpose of this study was to assess whether prophylaxis for digestive disorders with omeprazole is a risk factor for adverse drug events (ADEs) and kidney impairment.

**Methods:** This was a 9-month, prospective, double-blinded cohort study performed in a Brazilian public hospital. All inpatients 18 years or older admitted during the period of data collection were divided into 2 cohorts. The first group comprised 200 patients receiving prophylaxis for digestive disorders with omeprazole. A total of 54 inpatients who received treatment with omeprazole and whose indication was not approved by the Brazilian Sanitary Agency and the US Food and Drug Administration were excluded. The second group comprised 219 inpatients without a prescription for omeprazole. Follow-up was performed until discharge and included assessment of medical records, medical prescriptions, laboratory data, and pharmaceutical anamnesis. The primary end point was kidney impairment. The variables monitored were kidney function (serum creatinine and urea levels as well as glomerular filtration rate), hepatic function (alanine aminotransferase and aspartate aminotransferase levels), pharmacotherapy, magnesium levels, and imputation of ADEs. With the aid of algorithms of World Health Organization and the National Coordinating Council for Medication Error Reporting and Prevention, we assessed the causality of adverse drug reactions (ADRs) and the seriousness of medication errors (ADEs), respectively.

**Findings:** Prophylaxis for digestive disorders with omeprazole ($P = 0.019$) and sex ($P = 0.010$) were considered risk factors for increased serum creatinine level via multivariate logistic regression even with concomitant use of nephrotoxic drugs ($P = 0.252$). Six ADEs related to omeprazole were identified: 2 ADRs (1 possible and 1 definite), 2 medication errors (nonserious), 1 therapeutic failure, and 1 drug-drug interaction.

**Implications:** Prophylaxis for digestive disorders with omeprazole and male sex may contribute to the development of kidney impairment because both result in increased serum creatinine levels. Therefore, pharmacotherapeutic follow-up of male patients diagnosed with kidney disorders should be considered to identify potential drug-drug interactions early. This follow-up can prevent worsening clinical conditions and/or contraindicate prophylactic use of omeprazole. ClinicalTrials.gov identifier: NCT02278432. (*Clin Ther*. 2018;40:973–982) 

**Key words:** adverse drug events, kidney impairment, omeprazole, pharmacovigilance, risk management.

## INTRODUCTION

Omeprazole is one of the most frequently prescribed drugs worldwide because of its high effectiveness and low toxicity.[1] However, prescription of proton pump inhibitors (PPIs) is inappropriate for most patients, especially those who do not meet the clinical criteria of indication for which the drugs were approved.[2] Prescriptions for the off-label use of drugs increases

*Accepted for publication April 20, 2018.*
https://doi.org/10.1016/j.clinthera.2018.04.013
0149-2918/$ - see front matter

the risk of adverse drug events (ADEs) with potential costs for health institutions.[3]

Concerns regarding the tolerability of omeprazole have been expressed in the literature,[4] mainly because of conditions related to off-label use,[5,6] advanced age (>65 years of age, with concurrent diseases and polypharmacy),[5,7] and long-term use.[8] Therefore, on-demand therapy is more cost-effective than continuous therapy and should be considered whenever possible.[9]

Furthermore, studies have found an association between the use of PPIs and acute kidney injury (AKI). A meta-analysis found that the pooled adjusted risk relative (RR) of AKI in patients with PPI use was 1.61 (95% CI, 1.16–2.22; $I^2 = 98.1\%$).[10] According to Moledina and Perazella,[11] these cases are more common with omeprazole.

However, data on PPI-induced harm are discrepant between observational studies and randomized clinical trials (RCTs).[12] Observational studies allow assessment under uncontrolled conditions, including multiple outcomes, temporal relationships between the exposition and omeprazole, and patients with comorbidities. Several of these studies have found that concomitant long-term use of PPIs have adverse effects on patient morbidity and hospitalizations.[13,14]

However, Vaezi et al[15] suggest that data from these studies need to be regarded carefully. Overzealous conclusions based on weak associations between certain drugs and adverse effects can lead to inappropriate discontinuation of use of otherwise important and effective drugs. Moreover, many studies do not account for the disease burdens of the patients under study. Thus, disease burden may be a residual confounding factor within epidemiologic studies.[12,13] Other potential confounding factors, such as a lack of exact and uniform restrictions on PPI use as well as a lack indications and duration of the studies,[11] can also affect the risk of AKI. Thus, our study aimed to assess whether prophylaxis for digestive disorders with omeprazole is a risk factor for kidney impairment and ADEs.

## PATIENTS AND METHODS

### Study Design and Setting

This was a 9-month, prospective (August to October 2013 and December 2013 to May 2014) and double-blinded cohort study performed in a Brazilian medium-complexity public hospital with 30 clinical and surgical specialties and 104 beds. The variables of interest were recorded daily during the study period. The institution had an electronic records system for prescriptions, clinical outcomes, and laboratory parameters. All health professionals used this to record and update their assessments for each patient.

### Participants (Recruitment, Inclusion, and Exclusion Criteria)

Two cohorts were established with patients from the hospital under study. One cohort included inpatients who had been prescribed prophylaxis for digestive disorders with omeprazole. The other cohort included inpatients who did not use omeprazole. All inpatients 18 years or older and hospitalized during the data collection period were enrolled. Inpatients with a communication disability, such as intubation, cognitive impairment, or delirium, were excluded.

After recruitment, 219 inpatients not using omeprazole were designated as the nonomeprazole group. For those who had been prescribed omeprazole, we evaluated the indication of use. A total of 200 inpatients with prophylaxis for digestive disorders with 20 mg of omeprazole once daily while fasting met the inclusion criteria and were allocated to the omeprazole group.

We excluded 54 inpatients using omeprazole for treatments approved by the Brazilian Sanitary Agency and the US Food and Drug Administration, such as peptic ulcers, eradication of *Helicobacter pylori* infection, pathologic hypersecretory conditions, and erosive esophagitis. Both groups were followed until discharge.

### Variables

The primary medical outcome of the study was kidney impairment. We examined signs of kidney function impairment (eg, increasing serum creatinine level >1.2 mg/dL and a creatinine clearance glomerular filtration rate [GFR] <60 mL/min/1.73 $m^2$). We assessed potential triggers adapted from the Institute of Healthcare Improvement[16] to monitor and identify possible negative omeprazole-induced effects on the kidney (Table I).

Serum creatinine levels >1.2 mg/dL[17] and the a GFR <60 mL/min/1.73 $m^2$ were considered hallmarks of kidney impairment.[18] We used the Cockcroft-Gault and Jelliffe equations to calculate