

# Pharmacokinetic drug interaction profile of omeprazole with adverse consequences and clinical risk management

Wei Li<sup>1</sup>  
Su Zeng<sup>2</sup>  
Lu-Shan Yu<sup>2</sup>  
Quan Zhou<sup>3</sup>

<sup>1</sup>Division of Medical Affairs, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, People's Republic of China;

<sup>2</sup>Department of Pharmaceutical Analysis and Drug Metabolism, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, People's Republic of China; <sup>3</sup>Department of Pharmacy, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, People's Republic of China

**Background:** Omeprazole, a proton pump inhibitor (PPI), is widely used for the treatment of dyspepsia, peptic ulcer, gastroesophageal reflux disease, and functional dyspepsia. Polypharmacy is common in patients receiving omeprazole. Drug toxicity and treatment failure resulting from inappropriate combination therapy with omeprazole have been reported sporadically. Systematic review has not been available to address the pharmacokinetic drug-drug interaction (DDI) profile of omeprazole with adverse consequences, the factors determining the degree of DDI between omeprazole and comedication, and the corresponding clinical risk management.

**Methods:** Literature was identified by performing a PubMed search covering the period from January 1988 to March 2013. The full text of each article was critically reviewed, and data interpretation was performed.

**Results:** Omeprazole has actual adverse influences on the pharmacokinetics of medications such as diazepam, carbamazepine, clozapine, indinavir, nelfinavir, atazanavir, rilpivirine, methotrexate, tacrolimus, mycophenolate mofetil, clopidogrel, digoxin, itraconazole, posaconazole, and oral iron supplementation. Meanwhile, low efficacy of omeprazole treatment would be anticipated, as omeprazole elimination could be significantly induced by comedicated efavirenz and herb medicines such as St John's wort, *Ginkgo biloba*, and yin zhi huang. The mechanism for DDI involves induction or inhibition of cytochrome P450, inhibition of P-glycoprotein or breast cancer resistance protein-mediated drug transport, and inhibition of oral absorption by gastric acid suppression. Sometimes, DDIs of omeprazole do not exhibit a PPI class effect. Other suitable PPIs or histamine 2 antagonists may be therapeutic alternatives that can be used to avoid adverse consequences. The degree of DDIs associated with omeprazole and clinical outcomes depend on factors such as genotype status of CYP2C19 and CYP1A2, ethnicity, dose and treatment course of precipitant omeprazole, pharmaceutical formulation of object drug (eg, mycophenolate mofetil versus enteric-coated mycophenolate sodium), other concomitant medication (eg, omeprazole-indinavir versus omeprazole-indinavir-ritonavir), and administration schedule (eg, intensified dosing of mycophenolate mofetil versus standard dosing).

**Conclusion:** Despite the fact that omeprazole is one of the most widely prescribed drugs internationally, clinical professionals should enhance clinical risk management on adverse DDIs associated with omeprazole and ensure safe combination use of omeprazole by rationally prescribing alternatives, checking the appropriateness of physician orders before dispensing, and performing therapeutic drug monitoring.

**Keywords:** administration schedule, drug interactions, drug toxicity, herb-drug interactions, omeprazole, pharmacokinetics, polypharmacy, prescription auditing, risk management, treatment failure

Correspondence: Quan Zhou  
Department of Pharmacy, Second Affiliated Hospital, School of Medicine, Jiefang Rd No. 88, Zhejiang University, Hangzhou, Zhejiang 310009, People's Republic of China  
Tel +86 571 877 846 15  
Fax +86 571 870 227 76  
Email zhouquan142602@zju.edu.cn

## Introduction

Polypharmacy is a term used to describe the situation in which an individual patient is prescribed multiple medications. It often occurs because an individual patient, especially an elderly patient, may be under the care of multiple physicians: a patient who sees three different physicians may get three different prescriptions. These prescriptions may interact with each other, causing adverse drug reactions (sometimes dangerous ones) or reduced efficacy. Polypharmacy is not a problem in itself, but all too often there is a lack of coordination among care providers resulting in a risk for drug–drug interactions (DDIs).<sup>1–3</sup>

To guarantee safety in medication use, Joint Commission International requires that medication prescriptions or orders be reviewed for appropriateness before dispensing. Real or potential DDIs are one of the key elements included in the process toward appropriateness review.<sup>4</sup> For each DDI, the object drug is defined as the medication whose pharmacokinetics and/or pharmacodynamics may be modified by the drug interaction process. The precipitant drug is defined as the medication responsible for affecting the pharmacologic action or the pharmacokinetic properties of the object drug.<sup>5</sup>

Omeprazole is a proton pump inhibitor (PPI) used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease, laryngopharyngeal reflux, and Zollinger–Ellison syndrome. It is one of the most widely prescribed drugs internationally and is available over the counter in some countries. Polypharmacy is common in patients receiving omeprazole, and drug toxicity and treatment failure resulting from inappropriate combination therapy with omeprazole have been reported sporadically. DDI profiles of PPIs have been reviewed by Blume et al, Gerson and Triadafilopoulos, and Ogawa and Echizen.<sup>6–8</sup> However, these reviews mainly address the circumstance under which DDIs occurred when PPIs were precipitant drugs, although there also were sporadic studies of DDIs that occur when omeprazole was as object drug. Meanwhile, the factors determining the degree of DDI between omeprazole and comedication, the pharmacokinetic DDI profile of omeprazole with adverse consequences, and the corresponding clinical risk management have not been addressed systematically. Therefore, we here present an updated review on this issue.

## Methods

Relevant literature was identified by performing a PubMed search covering the period from January 1988

(the year omeprazole launched) to March 2013, using the search terms omeprazole and drug interaction and pharmacokinetics and additional filters (species: humans; languages: English). Three hundred and nineteen articles were detected. Inclusion criteria included studies describing omeprazole DDI with potential adverse consequences or inconsistent conclusions on clinical relevance. Exclusion criteria included studies that described omeprazole DDIs with therapeutic benefits or insignificant clinical relevance and studies that only addressed DDI issues of other PPIs, instead of omeprazole, but were still retrieved using the search terms. Sixty-three articles were finally included under this search strategy, using these inclusion/exclusion criteria.

In addition, we conducted a further review of the literature indicating that other PPIs and histamine 2 antagonists could be alternatives to omeprazole when significant DDIs occurred between omeprazole and combined medications. The full text of each article was critically reviewed, and valuable information was summarized by data interpretation.

## Results and discussion

Omeprazole has actual adverse influences on pharmacokinetics of medications such as diazepam, carbamazepine, clozapine, indinavir, nelfinavir, atazanavir, rilpivirine, methotrexate (MTX), tacrolimus, mycophenolate mofetil (MMF), clopidogrel, digoxin, itraconazole, posaconazole, and oral iron supplementation. Meanwhile, low efficacy of omeprazole treatment would be anticipated, as omeprazole elimination could be significantly induced by comedicated efavirenz and herb medicines such as St John's wort, *Ginkgo biloba*, and yin zhi huang (YZH). The mechanism for DDI involves induction or inhibition of cytochrome P450 (CYP), inhibition of P-glycoprotein, inhibition of breast cancer resistance protein-mediated drug transport, and inhibition of oral absorption by gastric acid suppression. Sometimes, DDIs of omeprazole do not exhibit a PPI class effect. Other suitable PPIs or histamine 2 antagonists may be therapeutic alternatives to avoid adverse consequences. The degree to which DDIs are associated with omeprazole and clinical outcomes depends on many factors such as genotype status of CYP2C19 and CYP1A2, ethnicity, dose, and treatment course of precipitant omeprazole, pharmaceutical formulation of the object drug, other concomitant medication, and administration schedule. Table 1 summarizes DDIs associated with omeprazole and clinical risk management.

## Circumstance I: omeprazole is comedicated as a precipitant drug

### Diazepam

#### DDI and risk description

Diazepam is commonly used for treating anxiety, panic attacks, insomnia, seizures, and muscle spasms. It undergoes extensive metabolism, primarily via CYP2C19-mediated demethylation. Omeprazole 40 mg once daily over the course of 7 days decreased diazepam plasma clearance from  $22.4 \pm 2.8$  to  $10.1 \pm 1.5$  mL/hour per kilogram body weight and prolonged the elimination half-life ( $t_{1/2}$ ) of diazepam from  $36.9 \pm 4.1$  to  $85.0 \pm 14.7$  hours. Plasma concentrations of the main metabolite desmethyldiazepam were reduced after omeprazole treatment because of CYP2C19 inhibition.<sup>9</sup> Inhibition of CYP2C19-catalyzed diazepam metabolism was estimated for omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole, using in vitro-derived inhibition parameters. The degree of inhibition varies across the PPIs, ranging from 79% (esomeprazole) and 46% (omeprazole) to less than 1% (pantoprazole and rabeprazole).<sup>10</sup>

The extent of the inhibitory effect of omeprazole on diazepam metabolism is dependent on ethnicity. The decrease in diazepam clearance and the prolongation in  $t_{1/2}$  of diazepam and desmethyldiazepam after pretreatment of omeprazole 40 mg once daily for 21 days were significantly greater in the Caucasian group than in the Chinese group.<sup>11</sup>

#### Clinical risk management

Combination use of the two drugs should be avoided in case of diazepam toxicity, with adverse effects such as confusion and ataxia. Pantoprazole, lansoprazole, and rabeprazole at the recommended doses do not significantly impair the metabolism of diazepam, and thus they are alternative PPIs for patients receiving diazepam without the need to adjust diazepam dosage.<sup>12-14</sup>

Oxazepam and lorazepam are two benzodiazepines that are not oxidatively metabolized by CYP but are glucuronidated by glucuronyl transferase, and therefore they are not subject to CYP-mediated metabolic inhibition. When clinically indicated, oxazepam and lorazepam may be the benzodiazepines of choice to use together with omeprazole.

## Carbamazepine

#### DDI and risk description

Carbamazepine is a widely prescribed antiepileptic drug. It undergoes extensive metabolism, primarily via

CYP3A4-mediated oxidation. It is possible for a patient with epilepsy who is receiving carbamazepine to also be receiving omeprazole because of gastrointestinal problems. Omeprazole is metabolized by CYP2C19 and CYP3A4, and carbamazepine is metabolized by CYP3A4, which can lead to competitive inhibition of carbamazepine metabolism. Multiple-dose administration of omeprazole (20 mg once daily) significantly altered the pharmacokinetics of carbamazepine in patients with duodenal ulcer (ie, increased area under the curve [ $AUC_{(0-\infty)}$ ] from 382.3 to 668.8  $\mu\text{g/mL}$  per hour, prolonged  $t_{1/2}$  from 17.2 to 37.3 hours, and decreased clearance from 20.7 to 12.5 mL/hour per kilogram body weight of carbamazepine).<sup>15</sup> A study by Dixit et al<sup>16</sup> noted that multiple-dose administration of omeprazole increased the peak concentrations ( $C_{\text{max}}$ ),  $AUC_{(0-\infty)}$ , and  $t_{1/2}$  of sustained-release carbamazepine in healthy male volunteers. Furthermore, combination use of omeprazole and carbamazepine could lead to decreased AUC of omeprazole because of the induction of CYP3A4 by carbamazepine.<sup>17</sup>

#### Clinical risk management

Therapeutic drug monitoring should be carried out when carbamazepine is coadministered with omeprazole. Pantoprazole is an alternative to omeprazole, as no dose adjustment of carbamazepine is required during concomitant use of pantoprazole at 40 mg once daily for 21 days.<sup>18</sup> Multiple doses of ranitidine do not alter single-dose carbamazepine pharmacokinetics in healthy adults; thus, it may be an alternative choice for acid suppression.<sup>19</sup>

## Clozapine

#### DDI and risk description

Clozapine is an atypical antipsychotic drug with a narrow therapeutic range. It is metabolized primarily by CYP1A2, an important determinant of clozapine dosage in patients with schizophrenia. Omeprazole is an inducer of CYP1A2 in vivo, and its inducibility of CYP1A2 is related to the genetic polymorphism of CYP1A2 and omeprazole dose.<sup>20,21</sup> Concomitant use of omeprazole reduced the plasma concentrations of clozapine by about 40% in patients with schizophrenia who received omeprazole in addition to clozapine because of gastrointestinal complaints.<sup>22</sup> The changes in the pharmacokinetics of clozapine are a result of the induction of CYP1A2 by omeprazole. Mookhoek et al<sup>23</sup> retrospectively evaluated the effect of omeprazole on clozapine metabolism in patients taking clozapine and omeprazole.

**Table 1** Drug–drug interactions associated with omeprazole and clinical risk management

Drug–drug interactions	Mechanism for drug–drug interactions	Clinical risk management
<b>Precipitant drugs</b>		
Diazepam	Omeprazole impairs CYP2C19-mediated demethylation of diazepam.	<ol style="list-style-type: none"> <li>1. Avoid such combination use in case of diazepam toxicity.</li> <li>2. Pantoprazole and lansoprazole are alternative proton pump inhibitors. Oxazepam and lorazepam are alternatives to use together with omeprazole.</li> </ol>
Carbamazepine	Omeprazole competitively inhibits CYP3A4-mediated carbamazepine metabolism.	<ol style="list-style-type: none"> <li>1. Therapeutic drug monitoring should be carried out when carbamazepine is coadministered with omeprazole.</li> <li>2. Select pantoprazole as an alternative proton pump inhibitor.</li> </ol>
Clozapine	Omeprazole induces CYP1A2-mediated clozapine metabolism.	<ol style="list-style-type: none"> <li>1. Close monitoring of plasma clozapine levels is recommended.</li> <li>2. Select pantoprazole as an alternative proton pump inhibitor.</li> </ol>
Indinavir, nelfinavir, atazanavir, and rilpivirine	Omeprazole decreases the solubility and absorption of indinavir, nelfinavir, atazanavir, and rilpivirine by increasing gastric pH. In addition, omeprazole competitively inhibits CYP2C19-mediated formation of nelfinavir's pharmacologically active metabolite.	<ol style="list-style-type: none"> <li>1. Indinavir: concomitant 200 mg ritonavir therapy may overcome the significant omeprazole–indinavir DDI. Cimetidine is an alternative to omeprazole.</li> <li>2. Nelfinavir: combination use of nelfinavir and proton pump inhibitor may be acceptable for indications where the proton pump inhibitor is required for fewer than 30 days.</li> <li>3. Atazanavir: increasing the atazanavir/ritonavir dose to 400/100 mg can attenuate the effect of omeprazole and warrant enough antiviral effect against wild-type HIV. Another option is to select alternative strategies for anti-HIV treatment that have a minimal risk of DDI with omeprazole.</li> <li>4. Rilpivirine: famotidine may be an alternative to omeprazole if spaced appropriately (ie, famotidine is administered 12 hours before or 4 hours after rilpivirine).</li> </ol>
MTX	Omeprazole blocks the active tubular secretion of MTX by the inhibition of renal elimination of hydrogen ion, as well as MTX efflux via the breast cancer-resistance protein in kidney-proximal tubules.	<ol style="list-style-type: none"> <li>1. Close therapeutic drug monitoring should be performed for patients receiving high-dose MTX therapy so as to decide whether to initiate the calcium folinate rescue therapy.</li> <li>2. A histamine 2 antagonist is recommended to substitute for a proton pump inhibitor, as concurrent therapy does not result in MTX toxicity.</li> </ol>
Tacrolimus	Omeprazole competitively inhibits a CYP3A4-mediated tacrolimus metabolism, especially in poor metabolizers for CYP2C19.	<ol style="list-style-type: none"> <li>1. Close therapeutic drug monitoring of tacrolimus should be carried out when starting or switching a proton pump inhibitor.</li> <li>2. Rabeprazole and pantoprazole are alternatives to omeprazole.</li> </ol>
MMF	Proton pump inhibitors reduce absorption of MMF by elevating gastric pH and decreasing dissolution of MMF.	<ol style="list-style-type: none"> <li>1. Pay more attention to monitoring mycophenolic acid levels in the presence of omeprazole, especially in the first week post-transplantation.</li> <li>2. Adopt a new strategy; that is, intensified dosing of MMF (1.5 g twice daily on days 1–5, then 1.0 g twice daily) instead of standard dosing (1.0 g twice daily).</li> <li>3. Enteric-coated mycophenolate sodium may be an alternative to MMF.</li> </ol>
Clopidogrel	Proton pump inhibitors competitively impair the metabolic activation of clopidogrel via CYP2C19 inhibition.	<ol style="list-style-type: none"> <li>1. Pantoprazole and rabeprazole are alternatives to omeprazole.</li> <li>2. PA32540 (a single-tablet formulation of 325 mg aspirin and 40 mg immediate-release omeprazole) and clopidogrel spaced 10 hours apart is a good strategy in comparison with synchronous administration of aspirin, clopidogrel, and omeprazole.</li> </ol>
Digoxin	Omeprazole induces the gastric permeability to digoxin and impairs the clearance by P-glycoprotein inhibition.	<ol style="list-style-type: none"> <li>1. Pantoprazole is an alternative to omeprazole when combination use of proton pump inhibitor and digoxin is needed.</li> <li>2. Monitor the serum concentrations and toxicity symptoms of digoxin in the presence of omeprazole, and adjust the dose of digoxin as needed.</li> </ol>

*(Continued)*

**Table I** (Continued)

Drug–drug interactions	Mechanism for drug–drug interactions	Clinical risk management
Itraconazole, posaconazole	Omeprazole reduces the pH-dependent absorption of itraconazole and posaconazole by suppressing gastric secretion.	<ol style="list-style-type: none"> <li>1. Avoid using proton pump inhibitors for patients receiving itraconazole or posaconazole.</li> <li>2. Monitor serum levels of posaconazole or switch to an alternative antifungal therapy if combination with omeprazole cannot be avoided. Histamine 2 antagonists have less interaction with posaconazole than proton pump inhibitors.</li> <li>3. Coadministration of an acidic solution (eg, a cola beverage) can counteract the adverse effect of gastric acid suppressants on the bioavailability of itraconazole.</li> </ol>
Oral iron supplementation	Omeprazole decreases the absorption of oral iron supplementation.	Iron-deficient patients taking proton pump inhibitors may have to be treated with high-dose iron therapy for a longer duration or with intravenous iron therapy.
<b>Object drug</b> Efavirenz, herbal medicines (St John's wort, <i>Ginkgo biloba</i> , yin zhi huang)	Efavirenz, St John's wort, and Yin zhi huang induce CYP2C19 and CYP3A activity and enormously accelerate omeprazole elimination. <i>Ginkgo biloba</i> can induce CYP2C19-mediated hydroxylation of omeprazole.	It seems inappropriate to prescribe omeprazole for patients receiving efavirenz, St John's wort, <i>Ginkgo biloba</i> , or yin zhi huang. Rabeprazole is an alternative proton pump inhibitor to omeprazole.

**Abbreviations:** CYP, cytochrome P450; DDI, drug–drug interaction; HIV, human immunodeficiency syndrome; MTX, methotrexate; MMF, mycophenolate mofetil.

After discontinuation of omeprazole therapy, all nonsmoking patients experienced a significant increase in serum clozapine concentrations compared with smokers, despite an unchanged daily dose of clozapine. The underlying mechanism for this interesting change was the disappearance of enzyme induction of CYP1A2 by omeprazole in nonsmokers after stopping omeprazole therapy, whereas CYP1A2 remained induced by smoking in patients who smoked.

### Clinical risk management

If patients are receiving omeprazole as comedication, close monitoring of plasma clozapine levels is recommended. Pantoprazole lacks induction of CYP1A2 activity in man,<sup>24</sup> and it may be an alternative to omeprazole when a PPI is added to clozapine therapy. However, caution should be exercised when omeprazole is replaced by pantoprazole and smoking cessation is required during hospitalization of smoking patients with psychosis who have been receiving omeprazole and clozapine. Otherwise, a strong increase in plasma clozapine concentrations will be observed because of the loss of the inducible effects on CYP1A2 of both smoking and omeprazole.<sup>25</sup>

### Anti-HIV-1 agents

The use of acid suppressants among human immunodeficiency virus (HIV)-infected patients is common and may potentially generate clinically significant DDIs that alter plasma

concentrations of anti-HIV-1 agents. It is important to understand the risk of these interactions, thereby maximizing antiviral potential and preventing HIV antiretroviral resistance.<sup>26</sup>

### DDI and risk description

As indicated by a retrospective analysis, patients receiving a combination of indinavir (800 mg three times daily) and omeprazole (20–40 mg daily) were susceptible to a lower plasma indinavir AUC than the average expected value in patients receiving indinavir alone.<sup>27</sup> Such pharmacokinetic changes can be explained by decreased indinavir solubility and absorption resulting from increasing gastric pH introduced by omeprazole.

Nelfinavir is metabolized mainly via CYP2C19 to nelfinavir hydroxy-t-butylamide, which exhibits potent antiviral activity. Omeprazole coadministration (40 mg daily for 4 days) significantly decreases the AUC values of nelfinavir in healthy participants. The main mechanism for this interaction was the suppression of gastric acid secretion, resulting in reduced nelfinavir solubility, and competitive inhibition of CYP2C19 by omeprazole, resulting in a reduction in pharmacologically active nelfinavir hydroxy-t-butylamide. Hence, omeprazole should not be coadministered to patients taking nelfinavir.<sup>28</sup>

Concomitant use of omeprazole and atazanavir is currently not recommended. Omeprazole 40 mg once daily significantly decreased atazanavir exposure by approximately 75%.

Even if atazanavir/ritonavir 300/100 mg were used, the addition of omeprazole still reduced atazanavir AUC and trough concentrations by 42% and 46%, respectively.<sup>29</sup> Rilpivirine, a non-nucleoside reverse transcriptase inhibitor, may have pharmacokinetic interactions with inducers and inhibitors of CYP3A4, which are drugs that increase gastric pH, and P-glycoprotein substrates. Rilpivirine should not be coadministered with PPIs in case of a significant reduction in rilpivirine absorption.<sup>30</sup>

### Clinical risk management

With respect to significant omeprazole–indinavir DDIs, concomitant 200 mg ritonavir therapy may reverse this adverse interaction, as it can substantially inhibit clearance of indinavir, presumably via mechanism-based inhibition of CYP3A-mediated metabolism of indinavir or, possibly, inhibition of P-glycoprotein.<sup>31–33</sup> As described in the package insert for Crixivan® (indinavir sulfate; Merck and Co, Inc, Whitehouse Station, NJ, USA), comedicated histamine 2 antagonist cimetidine (600 mg twice daily) minimally affected the AUC of a single 400 mg dose of indinavir. In situations in which both indinavir and cimetidine are indicated, cimetidine is an alternative in that its potent inhibitory effect on CYP3A may offset the influence of the elevated pH changes.<sup>34</sup>

For risk management of nelfinavir–omeprazole DDIs, it was suggested that combination use of nelfinavir and a PPI may be acceptable for indications in which the PPI is required for fewer than 30 days. A retrospective cohort study in 1147 HIV-positive adults receiving nelfinavir showed that the risk for virologic rebound was closely related with the time of exposure to the PPI. The hazard of virologic rebound resulting from short-term use of PPIs (defined as within 30 days of initial PPI dispensation) was 1.07 compared with no PPI exposure, whereas there was a 56% increased risk with long-term ( $\geq 30$  days) exposure to PPIs compared with the risk in the unexposed group ( $P = 0.02$ ).<sup>35</sup>

As far as risk management on atazanavir–omeprazole DDIs is concerned, increasing the atazanavir/ritonavir dose to 400/100 mg can attenuate the effect of omeprazole and warrant enough antiviral effect against wild-type HIV.<sup>29</sup> Another option is to select alternative strategies for anti-HIV treatment that have minimal risk for DDIs with omeprazole. For example, amprenavir plasma exposures were not altered when fosamprenavir (prodrug of amprenavir) and ritonavir 1400/200 mg were administered once a day in the morning and 20 mg omeprazole was given in the evening.<sup>36</sup>

If spaced appropriately, famotidine may be an alternative to PPIs for patients receiving rilpivirine. When famotidine

40 mg was administered 12 hours before or 4 hours after rilpivirine, rilpivirine pharmacokinetics were not significantly affected; such combination use is acceptable.<sup>37,38</sup>

## Methotrexate

### DDI and risk description

MTX is an antifolate agent used in the treatment of various cancers and some autoimmune diseases. It is frequently administered at a high dose in oncology and comes with various procedures to reduce the occurrence of toxicity and, particularly, to ensure optimal renal elimination. MTX is actively secreted in the distal tubules. A probable drug interaction between omeprazole and MTX was observed according to the Naranjo probability scale.<sup>39</sup> The proposed mechanism is that omeprazole can block the active tubular secretion of MTX through inhibition of renal elimination of the hydrogen ion and can inhibit breast cancer resistance protein–mediated efflux of MTX in human kidney proximal tubules. PPI coadministration independently increased the risk of delayed MTX elimination by 2.65 times.<sup>40</sup>

### Clinical risk management

Close therapeutic drug monitoring should be performed for patients receiving high-dose MTX therapy so as to decide whether to initiate the calcium folinate rescue therapy. A histamine 2 antagonist is recommended to substitute for a PPI, as concurrent therapy does not result in MTX toxicity.<sup>41</sup> For patients receiving high-dose MTX, transient discontinuation of the PPI or a switch for ranitidine should be proposed to avoid severe DDI, and similarly, a warning should be implemented when ranitidine (150 mg) is switched to omeprazole (20 mg daily, orally).<sup>42</sup>

## Tacrolimus

### DDI and risk description

Tacrolimus, an immunosuppressive drug, undergoes extensive hepatic metabolism largely via CYP3A4. In vitro studies using human liver microsomes have shown that omeprazole inhibits CYP3A4-mediated metabolism of tacrolimus competitively.<sup>43</sup> In the case of poor metabolizers (PMs) for CYP2C19, or if high doses of omeprazole (40 mg) are given to extensive metabolizers (EMs), CYP3A4 becomes the main enzyme for omeprazole elimination. The shared metabolism of omeprazole and tacrolimus through CYP3A4 has been associated with clinically significant drug interactions, especially in patients who are classified as PMs for CYP2C19.<sup>44</sup> The CYP2C19 polymorphisms, both in the native intestine and in the graft liver, have an effect on the

interaction between tacrolimus and omeprazole in adult living-donor liver transplant patients. The concentration/dose ratio of tacrolimus coadministered with omeprazole was significantly higher in patients with two variant alleles for CYP2C19 than those with the wild-type homozygote (CYP2C19\*1/\*1) or heterozygote (CYP2C19\*1/\*2 or CYP2C19\*1/\*3) ( $P = 0.010$  for native intestine;  $P = 0.022$  for graft liver).<sup>45</sup>

### Clinical risk management

Close therapeutic drug monitoring of tacrolimus should be considered when starting or switching a PPI in organ transplant recipients receiving tacrolimus-based immunosuppression. Esomeprazole and lansoprazole are also susceptible to interactions with tacrolimus.<sup>44,46</sup> Concomitant administration of rabeprazole or pantoprazole has insignificant influence on the pharmacokinetics of tacrolimus in adult transplant patients.<sup>47–49</sup>

## Mycophenolate mofetil

### DDI and risk description

MMF, an immunosuppressant and prodrug of mycophenolic acid (MPA), is used extensively in transplant medicine. MPA exposure by AUC correlates with the incidence of acute rejection episodes and transplant vasculopathy. Combination use of PPIs and MMF is possible because gastrointestinal adverse effects are common after organ transplantation. Unfortunately, PPI comedication could reduce active drug exposure in heart transplant recipients and renal transplant patients, thereby increasing the risk for treatment failure.<sup>50,51</sup>

### Clinical risk management

Optimization of administration schedule may be an option for managing DDIs between MMF and PPIs. Kiberd et al<sup>52</sup> presented a new finding that MPA pharmacokinetics were not significantly affected when an intensified dosing of MMF (1.5 g twice daily on days 1–5, then 1.0 g twice daily) instead of standard dosing (1.0 g twice daily) was used in combination with PPI therapy. This strategy may warrant adequate MPA exposure, whether or not a patient receives PPI comedication.

Omeprazole impairs the absorption of MMF, but not enteric-coated mycophenolate sodium (a formulation therapeutically equivalent to MMF), in healthy volunteers, indicating that impaired absorption of MMF with concomitant PPI is a result of incomplete dissolution of MMF in the stomach at elevated pH.<sup>53</sup> Therefore, enteric-coated mycophenolate sodium may be an alternative to immunosuppressant treatment.

David-Neto et al<sup>51</sup> presented the valuable finding that the mean AUC<sub>(0–12h)</sub> of MPA was in the lower limit of the therapeutic window on day 7 in patients using omeprazole but quickly increased on day 14 and thereafter, and that most patients were within the therapeutic window after day 7. This information is important for clinicians because there is a decreased incidence of acute rejection when the patients are adequately exposed to MPA during the first week. Clinicians should pay more attention to monitoring MPA levels in the presence of omeprazole, especially in the first week post-transplantation.

## Clopidogrel

### DDI and risk description

Clopidogrel is an oral antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Clopidogrel, along with aspirin, is considered the gold standard treatment for acute coronary syndrome by reducing the risk for new ischemic events; however, the dual therapy increases the risk for gastrointestinal bleeding. Therefore, comedicated PPI is recommended by most guidelines. Clopidogrel is a prodrug that needs to be converted to an active metabolite via hepatic activation, mainly through CYP2C19 and CYP3A4. As PPI metabolism also involves CYP2C19, it was assumed that PPIs might competitively interfere with clopidogrel's action.<sup>54,55</sup>

Most of the literature suggests that omeprazole is the PPI most likely to have a significant interaction with clopidogrel. However, in the Clopidogrel with or without Omeprazole in Coronary Artery Disease (COGENT) study, the authors randomly assigned patients ( $n = 3873$ ) with an indication for dual antiplatelet therapy to receive clopidogrel in combination with either omeprazole or placebo in addition to aspirin. It was concluded that prophylactic use of omeprazole reduced the rate of upper gastrointestinal bleeding (hazard ratio with omeprazole, 0.13;  $P = 0.001$ ) and that there was no apparent cardiovascular interaction between the two drugs (hazard ratio with omeprazole, 0.99;  $P = 0.96$ ).<sup>56</sup>

### Clinical risk management

To reduce the potential DDI between PPIs and clopidogrel, one option is to select a PPI that demonstrates relatively less influence on CYP2C19. Indeed, the clopidogrel–PPI interaction does not exhibit a PPI class effect.<sup>57</sup> Coadministration of rabeprazole and clopidogrel did not affect the antiplatelet efficacy of clopidogrel in healthy Chinese volunteers.<sup>58</sup> Neubauer et al<sup>59</sup> concluded that pantoprazole did not diminish the antiplatelet efficacy of clopidogrel. In situations in

which both clopidogrel and a PPI are indicated, pantoprazole should be used, as it is the PPI least likely to interact with clopidogrel.

Recently, a randomized study indicated that the use of dexlansoprazole or lansoprazole, rather than esomeprazole or omeprazole, could minimize the potential of PPIs to attenuate the efficacy of clopidogrel.<sup>60</sup> Concomitant use of famotidine 40 mg daily did not reduce the platelet inhibitory effect of clopidogrel in patients under dual antiplatelet therapy;<sup>61</sup> however, famotidine has not been proven effective for the prevention of upper gastrointestinal complications in patients receiving dual antiplatelet therapy.<sup>62</sup> Therefore, further investigation into the feasibility of switch to famotidine is needed.

Very recently, spaced administration of a clopidogrel and a single-tablet formulation of 325 mg aspirin and 40 mg immediate-release omeprazole (PA32540) was considered as an alternative that might reduce the potential pharmacodynamic interaction between omeprazole and clopidogrel. The spaced administration strategy involves a morning dosing of a single tablet of PA32540 followed 10 hours later by a 300-mg clopidogrel load on day 1, and then a morning dosing of a single tablet of PA32540 followed 10 hours later by 75 mg clopidogrel on day 2 and thereafter. The synchronous administration strategy is that 300 mg clopidogrel, 81 mg aspirin, and 40 mg omeprazole are dosed synchronously on day 1, and then 75 mg clopidogrel, 81 mg aspirin, and 40 mg omeprazole are given synchronously on day 2 and thereafter. The spaced therapy had greater antiplatelet effects than did the synchronous administration strategy ( $P = 0.004$ ).<sup>63</sup>

## Digoxin

### DDI and risk description

Digoxin is a medication widely used in treating heart failure. DDIs with digoxin are important because of this agent's narrow therapeutic index. The usual digoxin therapeutic range is 0.8–2 ng/mL. Omeprazole-associated digoxin toxicity has been observed in a 65-year-old Caucasian woman.<sup>64</sup> The patient was treated with digoxin at a dose of 0.625 mg daily for 6 years. Three months after initiation of omeprazole therapy (20 mg once daily), her serum digoxin level jumped from 1.1 to 3.9 ng/mL with normal hepatic and renal function. The possible mechanism for such an interaction may involve increased stomach absorption and impaired clearance by inhibition of P-glycoprotein. Omeprazole can induce the gastric permeability to digoxin,<sup>65</sup> and it can dose-dependently increase absorptive (apical-to-basal) digoxin permeability with maximal increases of 2.6-fold across human

colonic carcinoma cell line (Caco-2).<sup>66</sup> Omeprazole inhibits P-glycoprotein-mediated digoxin transport in Caco-2 cells with a half maximal inhibitory concentration ( $IC_{50}$ ) value of 17.7  $\mu$ M. In EMs of CYP2C19, the low dose of 20 mg omeprazole will result in a  $C_{max}$  of 1.5–3.5  $\mu$ M. In PMs of CYP2C19, plasma concentrations of omeprazole, especially at the 40 mg dose, would even reach the observed  $IC_{50}$  value. Therefore, it is assumed that PMs of CYP2C19 will be especially susceptible to the omeprazole/digoxin interaction.<sup>67</sup>

### Clinical risk management

Patients should be monitored for digoxin serum concentrations and signs of digoxin toxicity in the presence of omeprazole, and doses should be adjusted as needed. Pantoprazole 40 mg once daily for 5 days does not exhibit significant DDIs with digoxin in healthy volunteers, and these drugs may be administered concomitantly without the need for dose adjustment.<sup>68</sup>

## Antifungal agents

### DDI and risk description

The absorption of itraconazole is dependent on gastric acidity. Concomitant omeprazole treatment (40 mg once daily) for 2 weeks can significantly reduce the  $AUC_{0-24}$  and  $C_{max}$  of oral itraconazole capsules by 64% and 66%, respectively.<sup>69</sup> However, omeprazole 40 mg once daily for 7 days has no significant effect on the  $C_{max}$  of itraconazole oral solution.<sup>70</sup> This pharmacokinetic DDI difference may be attributed to the fact that itraconazole oral solution improved bioavailability and reduced pH dependency for adequate absorption when compared with capsules.

Posaconazole is an extended-spectrum triazole antifungal agent for the prevention and treatment of invasive fungal infections. Elevated gastric pH is accompanied by decreased posaconazole absorption. Omeprazole (40 mg once daily) for 3 days could significantly reduce posaconazole serum trough level.<sup>71</sup> When a higher dosage of omeprazole is used, this adverse effect could be profound and may result in therapeutic failure.

### Clinical risk management

Omeprazole and itraconazole capsule should not be used together. The two itraconazole formulations contain the same active ingredient, and it seems encouraging to substitute itraconazole oral solution for itraconazole capsule when coadministered with omeprazole. However, as described in package inserts, the two products have different indications and should not be used interchangeably. Fortunately, the

adverse effect of gastric acid suppressants on the bioavailability of itraconazole can be counteracted by the coadministration of an acidic solution (eg, a cola beverage) that transiently reduces the gastric pH.<sup>72</sup>

With respect to risk management of omeprazole–posaconazole DDIs, either serum levels of posaconazole should be monitored or antifungal therapy should be switched to an alternative agent if comedicated omeprazole cannot be avoided.<sup>71</sup> In patients with subtherapeutic posaconazole concentrations, increased dose frequency, administration with high-fat meals, and cessation of interacting medication use are useful strategies to improve systemic absorption.<sup>73</sup> Histamine 2 antagonists may have less interaction with posaconazole than PPIs. Posaconazole target attainment was associated with the use of histamine 2 antagonists over PPIs (odds ratio, 6.8).<sup>74</sup>

### Oral iron supplementation

Omeprazole, and possibly all PPIs, can decrease the absorption of oral iron supplementation. Physicians should be cognizant of an inadequate response to oral iron supplements by patients receiving PPIs. Iron-deficient patients taking PPIs may have to be treated either with high-dose iron therapy for a longer duration or with intravenous iron therapy.<sup>75</sup>

### Circumstance 2: omeprazole is comedicated as an object drug

Omeprazole is extensively metabolized in the liver through CYP2C19-mediated 5-hydroxylation and CYP3A4-mediated sulfoxidation reactions.<sup>76</sup> The low efficacy of the omeprazole treatment will be anticipated, as omeprazole elimination could be significantly induced by the following comedications.

#### Efavirenz

Efavirenz is a non-nucleoside reverse transcriptase inhibitor of HIV-1 reverse transcriptase used for the treatment of acquired immunodeficiency syndrome. In vitro studies have demonstrated that efavirenz could activate CYP3A4 and CYP2C19 promoter activity through the pregnane X receptor and the constitutive androstane receptor.<sup>77–79</sup> Repeated administration of efavirenz 600 mg daily can induce CYP2C19 and CYP3A activity and significantly decrease the  $AUC_{(0-\infty)}$  of omeprazole (about twofold) in healthy volunteers.<sup>80</sup>

#### St John's wort

St John's wort, an extract of the medicinal plant *Hypericum perforatum*, is widely used as a herbal antidepressant.

Receiving a 300 mg St John's wort tablet three times daily for 14 days can induce both CYP3A4-catalyzed sulfoxidation and CYP2C19-dependent hydroxylation of omeprazole, which enormously decreases the plasma concentrations of omeprazole. Omeprazole's bioavailability was significantly reduced in CYP2C19-genotyped EMs compared with PMs after long-term use of St John's wort.<sup>81,82</sup>

#### Ginkgo biloba

*Ginkgo biloba* is one of the most popular herbal medicines in the world. It has demonstrated remarkable pharmacological actions such as memory enhancing, cognition improving, and antiplatelet effects. Pharmacokinetic studies in healthy volunteers presented no herb–drug interaction between *Ginkgo biloba* extract and CYP2C19 substrates such as diazepam and voriconazole, indicating no evidence of induction of CYP2C19 activity by *Ginkgo biloba* treatment.<sup>83,84</sup> A cocktail interaction study in healthy volunteers demonstrated no relevant effect of *Ginkgo biloba* extract (240 mg daily for 8 days) on the in vivo activity of the major CYP enzymes in humans.<sup>85</sup> The first report of induction of CYP2C19-mediated hydroxylation by *Ginkgo biloba* in humans was presented by Yin et al.<sup>86</sup> *Ginkgo biloba* treatment (140 mg twice daily) for 12 days induced omeprazole hydroxylation in a CYP2C19 genotype–dependent manner (ie, the inducible effect was greater in PMs than EMs). The  $AUC_{(0-\infty)}$  ratios of omeprazole to 5-hydroxyomeprazole (an index of CYP2C19 activity) were decreased 42.3%, 50.3%, and 70.6% ( $P < 0.01$ ) in the homozygous EMs, heterozygous EMs, and PMs, respectively. Plasma concentrations of omeprazole and omeprazole sulfone were significantly decreased, and concentrations of 5-hydroxyomeprazole were significantly increased, after *Ginkgo biloba* administration. The observed interaction between *Ginkgo biloba* and omeprazole may be clinically important. The clinical efficacy and reduction of acid secretion with omeprazole is related to individual exposure to omeprazole.

#### YZH

Herbal medicine YZH, a decoction of yin chin (*Artemisia capillaris*) and three other herbs, is widely used in Asia to prevent and treat jaundice. Huang et al<sup>87</sup> demonstrated that YZH activated the constitutive androstane receptor (constitutive androstane receptor, NR1I3), which further increases CYP3A4 and CYP2C19 expression. In clinical use, YZH and omeprazole are often coadministered by patients with liver cirrhosis. Treatment of YZH oral liquid (10 mL three times daily for 14 days) enormously decreased

plasma concentrations of omeprazole and greatly increased those of omeprazole sulfone and 5-hydroxyomeprazole, indicating that YZH could induce CYP3A4-mediated sulfoxidation and CYP2C19-dependent hydroxylation of omeprazole.<sup>88</sup> CYP2C19\*2 homozygotes display a large degree of induction by YZH compared with CYP2C19\*1/\*1, CYP2C19\*1/\*2, and CYP2C19\*1/\*3 participants.  $AUC_{(0-\infty)}$  of omeprazole decreased by  $46.69\% \pm 17.82\%$  ( $P = 0.007$ ),  $41.38\% \pm 14.04\%$  ( $P = 0.002$ ), and  $16.25\% \pm 12.18\%$  ( $P = 0.039$ ) in CYP2C19\*1/CYP2C19\*1, CYP2C19\*1/CYP2C19\*2 or \*3, and CYP2C19\*2/CYP2C19\*2 participants, respectively. It can be postulated that YZH may lead to therapeutic failure or insufficient curative effect toward omeprazole in clinical situations because of pharmacokinetic variations.

### Clinical risk management

It seems inappropriate to prescribe omeprazole for patients receiving efavirenz, St John's wort, *Ginkgo biloba*, or YZH. Conversely, rabeprazole is metabolized mainly through a nonenzymatic pathway to rabeprazole-thioether and, to a much lesser extent, by CYP2C19 (demethylated rabeprazole) and CYP3A4 (rabeprazole-sulfone). Therefore, rabeprazole has a lower potential for DDIs.<sup>89,90</sup> It is assumed that DDIs between rabeprazole and any of the precipitant drugs mentioned earlier are absent, but this hypothesis needs to be verified by further investigation.

### Conclusion

In this review, we specially addressed DDIs associated with omeprazole with adverse consequences, the mechanisms for DDIs, the factors determining degree of DDI, and clinical risk management. Despite the fact that omeprazole is one of the most widely prescribed drugs internationally, clinical professionals should enhance clinical risk management on adverse DDIs associated with omeprazole and ensure safe combination use of omeprazole by rationally prescribing alternatives, checking the appropriateness of physician orders before dispensing, and performing therapeutic drug monitoring.

Suggestions for future research include that the quality of DDI studies be improved. For example, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, studies can be classified into high-quality (well-performed randomized clinical trials), moderate-quality (post hoc analysis of randomized clinical trials and propensity-matched studies), and low-quality (observational studies without propensity

matching) studies.<sup>91</sup> Meta-analyses report an inverse correlation between clopidogrel–PPI interaction and study quality ( $P = 0.007$ ), with high-quality and moderate-quality studies not reporting any association, increasing concerns about unmeasured confounders biasing the low-quality studies.<sup>54</sup> Adequately powered randomized controlled trials with pharmacodynamic evaluation are still needed to confirm the persisting doubts about the DDIs associated with omeprazole. In addition, investigations into factors determining the degree of DDIs as well as outcomes of clinical risk management and clinical pharmacy interventions should be strengthened.

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### Disclosure

The authors report no conflicts of interest in this work.

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