

CASE REPORT

Omeprazole Reduces Blood Level of Quetiapine

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CASE PRESENTATION

Mr. A is a 66-year-old single male with a long-standing history of schizoaffective disorder (SAD); his first related hospitalization was in 1960. Mr. A was recently admitted to hospital following the deterioration of his mental status and home situation. He was unable to maintain his apartment after his roommate moved to a nursing home. Prior to the current admission, Mr. A's SAD had been treated with first generation antipsychotics. During the present hospitalization, his medication was changed from haloperidol to quetiapine. The hope was that the patient would benefit from a better treatment response and suffer from fewer side effects with quetiapine. The patient responded well to the new treatment regimen, and his symptoms were well-controlled in hospital by quetiapine 600 mg daily. The blood level of quetiapine at this dose was 359 nmol/L. The authors have found, based on clinical experience, that patients generally require a quetiapine blood level of at least 200 nmol/L to show clinical improvement. After a few weeks of treatment, Mr. A had improved and was awaiting placement.

Several weeks into the hospital admission, Mr. A began complaining of heartburn and was started on omeprazole 20 mg daily. Within one week of starting omeprazole, he became psychotic, demonstrating increased agitation, confusion, excitability, decreased cognitive functioning and disorganized speech. Twelve days after the addition of omeprazole, given the deterioration in his mental status, the quetiapine dose was increased to 700 mg daily. Eight days later, his agitation persisted in spite of the increased quetiapine dose. Haloperidol 10 mg daily was added to his treatment regimen. Given persistent symptoms of heartburn three weeks into omeprazole treatment, the dose was increased to 40 mg daily. Mr. A's agitation settled following the increase in the quetiapine dose and the addition of haloperidol. However, he was not as well as he had been prior to starting omeprazole. The quetiapine blood level on 700 mg daily, measured 65 days

after starting omeprazole, was 104 nmol/L. Mr. A had not been using any other medications during this period.

CYTOCHROME P450 ENZYMES

One common way of metabolizing drugs involves the alteration of functional groups on the parent molecule (e.g., oxidation) via the cytochrome P450 enzymes (CYP450). The CYP450 system consists of a family of enzymes that are located on the smooth endoplasmic reticulum of cells throughout the body, with the highest concentrations being in the liver (hepatocytes) and small intestine,¹ and with the remainder being located in the lungs and other organs.² The CYP450 enzymes are heme-thiolate monooxygenases involved in the oxidative (Phase I) metabolism of a broad variety of both exogenous and endogenous compounds, including many medications.^{1,3} CYP450 enzymes account for 70 to 80% of enzymes involved in drug metabolism.

A substrate is an agent that is metabolized by an enzyme into a metabolic end product and eventually excreted. CYP450 enzymes use lipophilic drugs as substrates and biotransform these drugs to compounds that can be excreted by the kidneys. The metabolites are usually less active than the parent compound, although some drugs undergo biotransformation to pharmacologic active agents. In some cases the metabolites can be toxic, carcinogenic or teratogenic.⁴

The CYP450 enzymes are categorized into families based on amino acid sequence similarities, and these families are identified by Arabic numerals, placed directly after the CYP denomination. Each family can be further separated into subfamilies, which are designated by capital letters following the family designation (e.g., CYP3A).⁵ Individual enzymes are subsequently indicated by Arabic numerals (e.g., CYP3A4).⁴ Members of the CYP3A subfamily are the most abundant cytochrome enzymes in humans, accounting for 30% of the cytochrome enzymes in the liver and 70% of those in the intestine. CYP3A4 is the major form of CYP450 in the human liver and metabolizes the majority of xenobiotics.⁴

CYP3A4 and CYP3A3 are 97% identical and cannot be distinguished from each other based on the substrates that they metabolize. They are the major enzymes expressed in the small intestine. CYP3A5 is the major enzyme expressed in the stomach.⁶

Drug interactions involving the CYP450 system generally result from one of two processes: inhibition or induction of cytochrome P450 enzymes.⁴ An inhibitor is an agent which interferes with the ability of a given enzyme to metabolize a given substrate. The introduction of inhibitors generally leads to rapid increases in the blood levels of substrates. Competitive inhibition is the most common mechanism of inhibition, and occurs when two or more substances compete for the same enzyme. The importance of an inhibition interaction depends primarily on the relative concentrations of the drugs, as well as a variety of other patient-specific factors.

An inducer is an agent that causes an increase in the synthesis of the enzyme(s) responsible for metabolizing a given substrate, following exposure to a drug. Induction can occur when a drug stimulates the biotransformation of co-administered drugs either through the same enzyme pathway or via an alternative pathway. Inducers are usually specific for a given cytochrome P450 family.⁴ In certain situations, a drug can induce its own biotransformation in addition to that of other agents.

INTERACTIONS BETWEEN QUETIAPINE AND OMEPRAZOLE

Quetiapine, an atypical antipsychotic agent, is a dibenzothiazepine derivative and a multi-receptor antagonist. It is widely used in psychiatric practice as a first-line drug for psychoses and affective disorders. It is metabolized by the CYP450 3A4 isoenzyme via sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite.⁷ Both metabolites are pharmacologically inactive.⁷ CYP3A4 contributes 89% to the overall metabolism of quetiapine; the isoenzyme CYP2D6 plays a minor role.⁸

Proton pump inhibitors are the most potent inhibitors of gastric acid secretion available. Omeprazole, lansoprazole and pantoprazole are metabolized by several human CYP450 enzymes, primarily hepatic CYP2C19 (hydroxylation) and CYP3A4 (sulfoxidation).¹⁰⁻¹² Only pantoprazole is also metabolized by a sulfotransferase.⁹ Pantoprazole has the lowest potential for interactions, both in vitro and in human volunteer studies.⁹ Although the interaction profiles of esomeprazole, lansoprazole and rabeprazole have been less extensively investigated, evidence suggests that lansoprazole and rabeprazole have a lesser potential for interactions than omeprazole.^{9,10}

There are presently no reported interactions between omeprazole and quetiapine in the literature. This may be because omeprazole is predominantly metabolized by CYP2C19, and quetiapine by CYP3A4.^{11,13} However, interactions with other antipsychotics have been reported for

omeprazole.^{14,15} A retrospective study found that switching from omeprazole to pantoprazole resulted in a significant rise of the serum clozapine levels in non-smoking patients.¹⁶ This effect was likely due to the loss of CYP1A2 induction following discontinuation of omeprazole. Given that clozapine is metabolized by CYP3A4, CYP2D6 and CYP1A2, the loss of a CYP1A2 induction effect should increase the clozapine availability.¹⁷ Conversely, it was also reported that adding omeprazole for treatment of gastrointestinal complaints in two patients who had been receiving clozapine was associated with a reduction in the plasma levels of clozapine by 41.9% and 44.7% respectively.¹⁸ The decrease in the plasma concentrations of clozapine in the presence of omeprazole was considered to be due to the induction of CYP1A2. Another study performed in renal transplant recipients showed a significant increase in intestinal, but not hepatic, CYP3A4 activity after administration of omeprazole, whereas no change was noted after cimetidine or ranitidine administration.¹⁹ Given that it has previously been shown that 1) there is variable expression of CYP genes in the human small intestine, and 2) omeprazole can significantly increase the expression of CYPs 2A6, 2E1 and 3A4,²⁰ this study suggests that omeprazole induces intestinal CYP3A4 activity.¹⁹ Another case report showed that omeprazole significantly increased the concentration/dose ratio for tacrolimus without affecting liver function, thus suggesting involvement of intestinal cytochromes.²¹

RECOMMENDATIONS

1. Clinicians need to be vigilant about the possibility of a drug interaction between quetiapine and omeprazole.
2. If an undesirable drug interaction between omeprazole and quetiapine is suspected, the patient could be switched to a newer proton pump inhibitor such as pantoprazole, which has thus far demonstrated the lowest potential for drug interactions with quetiapine, or to an H₂-receptor antagonist such as ranitidine.

CASE REVISITED

After 65 days on omeprazole, the patient was switched to ranitidine 150 mg bid. One month later, his symptoms had largely resolved. Haloperidol was discontinued and the patient was discharged home on quetiapine 800 mg daily. The quetiapine blood level on this dose, measured 61 days after starting ranitidine, was 323 nmol/L. This value is lower than his initial blood level, measured on quetiapine 700 mg daily (359 nmol/L). A tentative explanation for this observation is that there was a residual effect of omeprazole. †

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