Changing Prescription Pattern of Omeprazole Among Patients Receiving Clopidogrel

Tarek KASHOUR,¹ MD, Mohamad AL-TANNIR,² DMD, and Reem BAHAMID,³ MSc

SUMMARY

Recent studies have suggested that omeprazole may reduce the inhibitory effect of clopidogrel on platelet aggregation. The United States Food and Drug Administration (FDA) has issued an update regarding this drug-drug interaction.

This study aimed to evaluate the changing prescription pattern of omeprazole in patients taking clopidogrel after the FDA update regarding the clopidogrel-omeprazole interaction.

A pharmacy database system was used to identify all prescriptions of clopidogrel alone, clopidogrel and omeprazole, or clopidogrel and ranitidine from May 1, 2009 until May 31, 2010.

A total of 2,899 prescriptions were entered into the final data analysis. There was a statistically significant drop in omeprazole prescription with clopidogrel from 46.6% in the period before the FDA update to 38.2% after the update ($P = 0.0037$). In addition, a significant increase was observed in the ranitidine prescription from 9.7% to 20.1% during the same time frame ($P = 0.0059$) without any significant change between the two study periods for those on clopidogrel alone without any protective gastrointestinal bleeding drug (43% versus 41.7%). On the other hand, of the 732 patients who were on clopidogrel and omeprazole during the period before the FDA update, 396 patients (54.1%) were taken off omeprazole, 274 (37.4%) were kept on both drugs, 59 (8.1%) had their omeprazole switched to ranitidine after the FDA update, and 3 patients were lost to follow-up (0.4%).

The present findings indicate a significant change in prescription pattern for omeprazole after the FDA update by taking patients off omeprazole or to a lesser extent replacing it with ranitidine. (Int Heart J 2014; 55: 93-95)

Key words: Proton pump inhibitor, H₂ blocker, Antiplatelet therapy, Ischemic, Percutaneous coronary intervention, Gastrointestinal bleeding, CYP450

Clopidogrel is used as an antiplatelet treatment for secondary prevention of acute coronary syndrome and prevention of stent thrombosis in patients undergoing percutaneous coronary intervention (PCI).¹ Several studies have shown variability in the biological response to clopidogrel and its clinical relevance.¹⁻³ However, the mechanisms underlying this variability remain controversial and multiple factors seem to be involved.⁴⁻⁶ These include drug interactions involving the cytochrome P450 (CYP450), insulin resistance, poor bioavailability, and polymorphisms of the CYP450 and P2Y₁₂ receptor genes.^{4,5}

Proton pump inhibitors (PPI) are usually given to patients receiving antiplatelet therapy to prevent gastrointestinal symptoms and are metabolized mainly by the CYP450.^{1,7} Different observational studies showed significant cardiovascular adverse events arising from a potential drug interaction due to concomitant use of clopidogrel and PPIs.^{1,4,5,8-10} The inhibitory effect of omeprazole on the antiaggregation effects of clopidogrel is most pronounced among the various PPIs studied.¹¹ The postulated mechanism underlying this interaction is competitive hepatic metabolism of clopidogrel and omeprazole by

the CYP450 system, leading to reduced levels of the active clopidogrel metabolite.⁸ Loss-of-function polymorphisms in the CYP450 genes may also reduce clopidogrel metabolism and are therefore likely to intensify interactions between drugs metabolized by the CYP450 system.^{9,10}

Thus, The United States Food and Drug Administration (FDA) and the European Medicines Agency have recommended that physicians avoid the use of omeprazole in all patients taking clopidogrel.^{12,13}

Various studies have examined the impact of the FDA warnings on the prescription pattern of some drugs such as droperidol, cisapride, antipsychotics and antidepressants, and glucose lowering drugs.¹⁴⁻¹⁶

Thus, we conducted this observational study to explore the changing prescription pattern of omeprazole among patients receiving clopidogrel after the FDA update regarding the clopidogrel-omeprazole interaction.

From the ¹ Department of Interventional Cardiology, Cardiac Center, King Khalid Hospital, ² Department of Clinical and Applied Research, Research and Publication Center, and ³ Prince Salman Heart Center, King Fahad Medical City, Riyadh, Saudi Arabia.

Address for correspondence: Tarek Kashour, MD, Department of Cardiology, King Saud University College of Medicine P.O. Box 7805 (92) Riyadh, 11472 Kingdom of Saudi Arabia. E-mail: tkashour@gmail.com

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Table. Prescription Patterns From May 2009 to May 2010

Time period	May- October, 2009	December, 2009-May, 2010	P
Omeprazole & Clopidogrel	732 (46.65%)	508 (38.2%)	0.0037
Ranitidine & Clopidogrel	154 (9.7%)	267 (20.1%)	0.0059
Clopidogrel only	686 (43%)	552 (41.7%)	0.27

METHODS

Study design: A pharmacy database system was used to identify all prescriptions of clopidogrel alone, clopidogrel and omeprazole, or clopidogrel and ranitidine from May 1, 2009 until May 31, 2010 at King Fahad Medical City, Riyadh, Saudi Arabia, which is one of the largest tertiary care centers in Saudi Arabia. Prior approval to conduct this study was obtained from the Institutional Review Board.

We compared the prescription pattern for 6 months before the FDA update (May 1, 2009 to October 31, 2009) to 6 months after the FDA update (December 1, 2009 to May 31, 2010). We excluded November 2009 from the final analysis as it was considered to be the transition month between the two periods.

Statistical analysis: Data were extracted and cleaned using Structured Query Language 2008 and Excel 2007. Frequency analysis was performed using Stata 10. The Z-test was used to calculate *P* values.

RESULTS

A total of 2,899 prescriptions for patients with acute coronary syndrome, unstable angina, ST segment myocardial infarction (STEMI), or non-STEMI were entered into the final data analysis.

Overall, a substantial number of clopidogrel prescriptions from May 2009 to May 2010 were without concomitant gastrointestinal protection agents. Furthermore, there was a statistically significant decrease in the percentage of concomitant omeprazole and clopidogrel prescriptions from 46.6% in the period before the FDA update to 38.2% after the FDA update ($P = 0.0037$) (Table). In addition, a significant increase was observed in the percentage of ranitidine prescriptions from 9.7% to 20.1% between the two time periods ($P = 0.0059$). In contrast, no significant difference among the prescriptions of clopidogrel was observed.

Moreover, follow-up results showed that among the 732 prescriptions of combined therapy consisting of clopidogrel and omeprazole during the 6-month period before the FDA update, 397 patients (54.1%) were taken off omeprazole, 274 patients (37.4%) were kept on both drugs, and only 59 (8.1%) had their omeprazole switched to ranitidine after the FDA update. Three patients (0.4%) were lost to follow-up (Figure).

DISCUSSION

The results of this study showed that there was a significant decrease in the prescription of omeprazole among all patients taking clopidogrel after the FDA statement in November

Total number of patients 732

- ▲ Patients on clopidogrel and omeprazole after FDA update ($n = 274$)
- Patients off omeprazole after FDA update ($n = 396$)
- Lost to follow up ($n = 3$)
- Patients switched from omeprazole to ranitidine after FDA update ($n = 59$)

Figure. Percentage of patients who were on omeprazole and clopidogrel from May to October, 2009 and continuing on treatment from December, 2009 to May, 2010.

2009 that recommended against the concurrent use of clopidogrel and omeprazole. This change resulted in a concomitant increase in ranitidine among patients undergoing PCI or with an acute coronary syndrome within the cardiac center at King Fahad Medical City. Moreover, a considerable number of patients were taken off omeprazole during the 6-month period following the FDA update and left unprotected despite their considerable risk of gastrointestinal bleeding.

The published data from different studies showed controversial results regarding clopidogrel and PPI.^{2,3} Some of the studies confirmed an interaction between clopidogrel and PPI.^{4,5,8-10} Kyeong, *et al* found that the P2Y₁₂ reaction unit (PRU) of omeprazole treated subjects was significantly higher than that of the omeprazole untreated subjects and the percentage inhibition decreased in the omeprazole treatment versus no omeprazole treatment.⁴ Moreover, it has been found that patients taking clopidogrel plus a PPI had a higher risk of hospitalization for recurrent acute coronary syndrome compared with patients taking clopidogrel without a PPI.¹⁰ All these provided the evidence to comply with the FDA update. A randomized controlled trial showed a significant reduction in gastrointestinal events in the omeprazole group, but no differences in cardiovascular events between the two groups, and claimed there was no clinically relevant adverse cardiovascular interaction between clopidogrel and PPIs.¹⁷ This discrepancy mandates evaluation with higher powered, prospective, randomized, controlled clinical trials that are necessary to confirm if omeprazole has any clinical effect on the antiplatelet effect of clopidogrel.

With this conflicting evidence, the FDA release might be untimely since it did not include the results of the clopidogrel and the Optimization of Gastrointestinal Events trial.¹⁷ Additionally, it has been suggested that the degree of the interaction between clopidogrel and PPIs is not homogeneous within the class of PPIs and is less marked with pantoprazole than with omeprazole. Thus, it is not clear if the interaction of omeprazole with clopidogrel is the same as with all PPIs (class effect) or if it is restricted to a subgroup of PPI (drug effect). This situation is likely dividing physicians treating cardiac patients into two camps regarding their belief in the presence of a clinically

significant interaction between clopidogrel and proton pump inhibitors. Our results showed a high rate of physician compliance with the FDA update.

The major limitation of this study is that it is an observational, retrospective, single center study. It is also a short-term study and did not include any clinical outcomes. However, the focus of the study is on prescription pattern changes in response to the FDA warning rather than its outcome implications. Our analysis included only omeprazole and not other proton pump inhibitors. This is because it is the only PPI available in our pharmacy; therefore, this should not affect the overall results of our study.

Patients who went off omeprazole must be kept on another gastrointestinal protector if they have any risk factors such as a history of gastrointestinal bleeding, dual antiplatelet therapy, or concurrent use of clopidogrel with an anticoagulant, or if they have more than one of the following risk factors; age more than or equal to 60 years, corticosteroid use, dyspepsia, or gastrointestinal esophagus reflex symptoms as per the ACCF/ACG/AHA Expert Consensus Document.⁷⁾

Regrettably, our data could not identify those with any risk factors for gastrointestinal bleeding.

In conclusion, this observational study adds to the existing body of evidence that warnings from regulatory bodies like FDA do affect prescription practices among physicians. It remains to be established, by conducting well designed clinical trials, whether such a change in prescription pattern affects patient outcomes.

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