



Keywords

Clopidogrel,
Plavix,
Proton Pump Inhibitors,
PPIs,
P₂Y₁₂,
Anticoagulant,
Drug interactions

Received: May 27, 2014

Revised: June 23, 2014

Accepted: June 24, 2014

Investigational study for the effect of some Proton Pump Inhibitors on the anticoagulant effect of Clopidogrel

Mootaz M. Salman^{1,*}, Al-mashhadany Mohammed S.^{2,*},
Kalandar Ola O.³, Yashaswini Srinivas⁴

¹Biomedical Research Center, Sheffield Hallam University, Sheffield, UK

²FICMS Cardiothoracic and vascular surgery, Al-Salam Teaching Hospital, Mosul, Iraq

³Clinical Pharmacist, Al-Salam Teaching Hospital, Mosul, Iraq

⁴Research associate-Pharmacology at Indfrag Limited, India

Email address

mootaz.m.salman@student.shu.ac.uk (M. Salman)

Citation

Mootaz M. Salman, Al-mashhadany Mohammed S., Kalandar Ola O., Yashaswini Srinivas. Investigational Study for the Effect of Some Proton Pump Inhibitors on the Anticoagulant Effect of Clopidogrel. *American Journal of Pharmacy and Pharmacology*. Vol. 1, No. 2, 2014, pp. 12-16.

Abstract

Clopidogrel is a mainstay therapy in the cardiovascular (CVS) pharmacology for the prevention of the stent thrombosis and myocardial infarctions following many different types of coronary syndromes. The conversion of clopidogrel; which is a prodrug, to its active metabolite is mediated by the cytochrome P450 (CYP). The CYP450 metabolic activation of clopidogrel has proposed about if the competition and/or the inhibitor medications for these isoenzymes may reduce or limit the clopidogrel therapeutic effectiveness. The identification of such an impact will be of the higher importance with the group of drugs called the Proton Pump Inhibitors (PPIs) as many of which are CYP3A4 inhibitors. Unless for the Omeprazole. Limited numbers of non-confirmed data were existed concerning the influence of the interaction between the other PPIs (such as Rabeprazole and Pantoprazole) and the therapeutic effectiveness of clopidogrel. This study sought to examine the effects of PPI's pantoprazole and rabeprazole co-administered with clopidogrel in patients with ischemic heart disease and peripheral vascular disease. Our clinical research data show that platelet aggregation was significantly higher in patients who were under rabeprazole treatment at the time of the platelet function test; on the other hand, such attenuating effect on the platelet response to clopidogrel was not seen in patients on pantoprazole. Till further evidence becomes available, patients on clopidogrel maintenance therapy should be reevaluated for PPI use. Those having well-controlled symptoms may be candidates for either Rabeprazole or pantoprazole. Patients with history of gastrointestinal bleed will require gastroprotection in the form of PPIs. In such cases, pantoprazole should be the preferred PPI.

1. Introduction

The platelet function inhibitor; clopidogrel that is a thienopyridine P₂Y₁₂ inhibitor, is a mainstay therapy in the cardiovascular (CVS) pharmacology for the prevention of the stent thrombosis and myocardial infarctions following many different types of acute percutaneous and coronary syndromes (Savi, et al., 1992; Majerus and Tollefsen, 2006).

The P₂Y₁₂ protein exists majorly but not particularly on the platelet surfaces and it is considered to be the cornerstone factor in the blood-clotting mechanism (Yusuf, et al., 2001).

Despite the fact that there are many risk factors that play an established role in the recurrence of CVS event, platelet reactivity is still to be one of the most dangerous factors for that in many patients, in spite of being on an antiplatelet medication such as clopidogrel (Zairis, et al., 2010; Zuern, et al., 2010).

The conversion of clopidogrel; which is a prodrug, to its active metabolite is mediated by the cytochrome P450 (CYP) through the incorporation of a number of isoenzymes CYP3A4, CYP1A2, CYP2C9, CYP2C19, and/or CYP2B6 (Rassen, et al., 2009; Savi, et al., 2000).

The CYP450 metabolic activation of clopidogrel has proposed about if the competition and/or the inhibitor medications for these isoenzymes may reduce or limit the clopidogrel therapeutic effectiveness, particularly through CYP2C19 (Aubert, et al., 2008), the thing that has been proposed by a number of studies via ex-vivo platelet function measurements; however, the clinical outcomes of such studies were hard to be proved (Lau, et al., 2003; Saw, et al., 2003). The identification of such an impact will be of the higher importance with the group of drugs called the Proton Pump Inhibitors (PPIs) as many of which are CYP2C19 inhibitors (O' Donoghue, et al., 2009). PPIs are considered to be first line in the pharmacotherapeutic of the gastro-intestinal tract (GIT) complication prevention in the patients with high risk factors or previous history and accordingly both of PPIs and clopidogrel are considered to be on of the most commonly prescribed drugs all over the world, which are overwhelmingly co-administered (Shrestha, et al., 2011). Information for the healthcare-professionals regarding the updates of clopidogrel labeling and its interaction with Omeprazole; a prototype of PPIs drugs, has been issued by the Food and Drug Administration (FDA) which include the following considerations:

- "The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel active metabolite levels and anticlotting activity.
- Other drugs that should be avoided in combination with clopidogrel because they may have a similar interaction include esomeprazole and cimetidine.
- At this time, FDA does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations".

Following a comprehensive literature search through a PubMed/MEDLINE database, we have found that the vast majority of the retrospective cohort studies and other studies utilizing platelet biomarkers have been demonstrated a significant relationship between the reduced clopidogrel therapeutic effectiveness and the co-utilization

of PPIs and in particular Omeprazole while a limited number of clinical comparative studies found that there was no link between the same (Dunn, et al., 2008; Li, et al., 2004; Sibbing, et al., 2009; Saw, et al., 2009; Kashour, et al., 2014).

Consequently, limited numbers of non-confirmed data were existed concerning the influence of the interaction between the other PPIs (such as Rabeprazole and Pantoprazole) and the therapeutic effectiveness of clopidogrel.

This will be the major focus of our study to provide a useful guideline especially for our locality.

This study sought to examine the effects of PPI's pantoprazole and rabeprazole co-administered with clopidogrel in patients with ischemic heart disease and peripheral vascular disease.

2. Methodology and Results

An association could exist between the use of PPIs especially omeprazole and the decrease in the antiplatelet efficacy of clopidogrel as evident by most of observational studies (Juurlink, et al., 2009). But the causal relationship and its clinical significance could not be ascertained due to conflicting results shown by prospective studies using clinical outcomes (O' Donoghue, et al. 2009; Bhatt, et al., 2010). In addition to limitations of observational studies, certain questions can be raised regarding ex vivo platelet assay studies. Atorvastatin was found to reduce the antiplatelet efficacy of clopidogrel in an ex vivo study which was proven clinically insignificant (Lau, et al., 2003; Saw, et al., 2003).

100 patients were selected for the study at Al—Salam teaching hospital, Mosul, Iraq. The hospital consultations were held in the cardiovascular department between 1st March to 1st July 2013.

The total number of patients were divided into 2 groups and studied. All the patients were enrolled into the study after performing physiological investigations such as ECG & echocardiography; Doppler study; blood urea; blood sugar (11 diabetics); lipid profile (32 hyperlipidaemics) and hematological investigations. Patients were diagnosed with ischemic heart disease, peripheral vascular occlusive disease; all were given 75 mg clopidogrel of the same company after establishing the diagnosis.

The first group consists of 50 patients (42 males and 8 females) with no Aspirin or clopidogrel drug history; 35 of them with IHD and the rest 15 patients had PVD. The average age of this group was 58.6. A drug treatment of 75 mg clopidogrel has been started with them. The average of their physiological investigational parameters range were normal and nearly to be like that [(165-345) for the platelet count; (30-35 seconds) for aPTT and an average of 12 seconds for the prothrombin time and 106 seconds for P₂Y₁₂].

The physiological investigations for our biomarker of

interest; P_2Y_{12} , were done in the 2nd or 3rd day from the clopidogrel therapy-starting day. Their results show a very good response to clopidogrel therapy reflected by the increment of P_2Y_{12} to 300 seconds for 36 of them and 250 seconds to 12; while 2 of them does not relatively show any difference. The utilized clopidogrel was well tolerated and there were no allergic or bleeding side effects.

Then the second group 50 patients almost the same criteria 34 patients with ischemic heart disease & 16 patients with peripheral vascular occlusive disease, 15 were diabetics, all with no history of aspirin or clopidogrel use, also we started clopidogrel 75 mg and we did P_2Y_{12} receptor time in the 2nd or 3rd day all of them reach 300 seconds this group subdivided into 2 groups of 25 patients. The first group was subjected to Rabeprazole 20 mg after 3rd day of clopidogrel ingestion while the second one was subjected to Pantoprazole 20 mg after 3rd day of clopidogrel ingestion, for both group PPI were added for gastrointestinal upset or GERD. The physiological investigations for our biomarker of interest; P_2Y_{12} , were done in the 2nd or 3rd day from the addition of PPIs.

The results for the first subgroup of the second group showed that the time of P_2Y_{12} receptors was returned to 165 seconds for 13 of them while it returned to 200 seconds for the rest of 12. On the other hand, the results of the second subgroup showed that there is no much difference in the time for the majority of them as it was returned for 275 seconds for 19 of them; while it returned to almost the average of 200 to the rest of 6 patients.

3. Discussion

The CYP2C19 mediates the conversion of the prodrug clopidogrel to its active thiol metabolites that eventually inhibit platelet P_2Y_{12} -ADP receptors (Savi, et al., 2000). This enzyme can also be inhibited by most PPIs for their main metabolic-processes pathway. Thus, the co-administration of PPIs decreases the process of clopidogrel conversion to its active metabolites and hence minimizing its desired therapeutic role of antiplatelet action.

The diversity of the sample age, sex, physiological parameters and past medical history was an added point for the honesty of our study as we want to get a random sample that match our research criteria without any bias.

The first outcome that can be concluded from this study is the good response from the majority of our sample to the antiplatelet effect of clopidogrel; the thing that considered to be a confirmative data for its effect and additionally as an indication for the good quality of the utilized brand. Despite the fact that they are a minority, health care professional should take in account the 2 patients who did not show any response to clopidogrel as the administration of this drug is a life saving intervention in a number of serious medical conditions such as MI; IHD and thromboembolism which could open the door to thinking about the role of pharmacogenomics of this drug (Brandt, et al., 2007).

There is a high variability in the clopidogrel

pharmacological effects regarding cellular, clinical and genetic factors; especially for the CYP2C19 enzyme that could have a dramatic effect on the therapeutic response to clopidogrel (O' Donoghue, et al., 2009). This enzyme demonstrates genetic polymorphism with 3-24% Asian and 3-6 Caucasian being poor-metabolizers (Bertsson, 1995; Destal, et al., 2002; Hokimoto, et al., 2014).

Patients having CYP2C19 loss of functional alleles expressed decreased levels of clopidogrel active metabolite, subjecting them to 3 times higher risk factor for different CVS events (Simon, et al., 2009; Hokimoto, et al., 2014).

P_2Y_{12} is an adenosine diphosphate (ADP) chemoreceptor and it is a member of Gi class from the major family of G protein coupled receptors (GPCR) of purigenic type. This P_2Y family has different selectivity prosperities that could sometimes overlaps for various uridine and adenosine nucleotides. This receptor is engaged in the vital process of platelet aggregation, which makes it a valuable target for the treatment of many clotting diseases such as thromboembolism (Gilard, et al., 2008). Interestingly for this gene, two transcriptional variants that encoding the exact isoform have been recognized which again strongly suggest the further role of pharmacogenetics in the understanding the unusual response of some patients regarding the clopidogrel treatment comparing to others.

Our clinical research data show that platelet aggregation was significantly higher in patients who were under rabeprazole treatment at the time of the platelet function test; on the other hand, such attenuating effect on the platelet response to clopidogrel was not seen in patients on pantoprazole.

Pantoprazole was not associated with a decrease in the antiplatelet efficacy of clopidogrel. Patients with a history of gastrointestinal bleed will require gastroprotection in the form of PPIs. We can suggest that, in such cases, pantoprazole should be the preferred PPI. Rabeprazole can be used as an alternative (Funck-Brentano, et al., 2013).

In conclusion, till further evidence becomes available, patients on clopidogrel maintenance therapy should be reevaluated for PPI use. Those having well-controlled symptoms may be candidates for either Rabeprazole or pantoprazole. Patients with history of gastrointestinal bleed will require gastroprotection in the form of PPIs. In such cases, pantoprazole should be the preferred PPI. Rabeprazole is less likely to inhibit CYP 2C19; so it is a good alternative. This is in accordance with the Juhasz and his colleagues' findings (Juhasz, et al., 2010).

Recommendations and Acknowledgement

We do recommend the utilization of the P_2Y_{12} test in all our hospitals in order to follow up the patients in such a serious cardiovascular conditions and also to be sure regarding the therapeutic efficacy of these life-saving drugs specially after the evidences of clopidogrel resistance and

receptor polymorphism.

The authors would like to gratefully acknowledge Pioneer Pharmaceutical company for helping out this research and the patients by providing the required medicines of clopidogrel (Plavineer® 75) to our entire sample.

The correspondent author is also grateful to the Higher Committee for Education Development in Iraq (HCED/Iraq) for sponsoring him during his PhD study at Sheffield Hallam University.

References

- [1] Aubert RE, Epstein RS, Teagarden JR. Abstract 3998: Proton pump inhibitors effect on clopidogrel effectiveness: The Clopidogrel Medco Outcomes Study. *Circulation* 2008; 118: S815.
- [2] Bertilsson L. Geographical/interracial differences in polymorphic drug oxidation. Current state of knowledge of cytochromes P450 (CYP) 2D6 and 2C19. *Clin Pharmacokinet* 1995; 29: 192-209.
- [3] Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FK, Furberg CD, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008; 118: 1894-09.
- [4] Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010; 363:1909-17.
- [5] Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS 2 nd , Lachno DR, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost* 2007;5:2429-31.
- [6] Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet* 2002;41:913-58.
- [7] Dunn SP, Macaulay TE, Brennan DM. Baseline proton pump inhibitor use is associated with increased cardiovascular events with and without the use of clopidogrel in the CREDO trial. *Circulation* 2008;118:815A.
- [8] Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: The randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008;5:256-60.
- [9] Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009;301:937-44.
- [10] Juhász M, Herszényi L, Tulassay Z. Current Standings of the Proton Pump Inhibitor and Clopidogrel Co-Therapy: Review on an Evolving Field with the Eyes of the Gastroenterologist. *Digestion* 2010;81:10-5.
- [11] Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009;180:713-8.
- [12] Label of Plavix (Clopidogrel bisulphate). [Updated on 2010 mar 12] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s0421bl.pdf . [accessed on 2014 mar 16].
- [13] Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: A new drug-drug interaction. *Circulation* 2003;107:32-7.
- [14] Li XQ, Andersson TB, Ahlström M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metab Dispos* 2004;32:821-7.
- [15] Majerus PW, Tollefsen DM. Drugs acting on blood and blood forming organs; blood coagulation and anti-coagulant, thrombolytic, and antiplatelet drugs: Introduction. In: Brunton LL, Lazo JS, Parker KL, editors. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 11 th ed. McGraw-Hill: New York; 2006. p. 1467-88.
- [16] O'Donoghue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: An analysis of two randomised trials. *Lancet* 2009;374:989-97.
- [17] Rassen JA, Choudhry NK, Avorn J, Schneeweiss S. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome. *Circulation* 2009;120:2322-9.
- [18] Savi P, Herbert JM, Pflieger AM, Dol F, Delebassee D, Combalbert J, et al. Importance of hepatic metabolism in the antiaggregating activity of the thienopyridine clopidogrel. *Biochem Pharmacol* 1992;44:527-32.
- [19] Savi P, Pereillo JM, Uzabiaga MF, Combalbert J, Picard C, Maffrand JP, et al. Identification and biological activity of the active metabolite of clopidogrel. *Thromb Haemost* 2000;84:891-6.
- [20] Saw J, Steinhubl SR, Berger PB, Kereiakes DJ, Serebruany VL, Brennan D, et al. Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. *Circulation* 2003;108:921-4.
- [21] Sibbing D, Morath T, Stegherr J, Braun S, Vogt W, Hadamitzky M, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. *Thromb Haemost* 2009;101:714-9.
- [22] Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360:363-75.
- [23] Update to the labeling of Clopidogrel Bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC). Available from: <http://www.fda.gov/Drugs/...../ucm190787.htm> . [Updated on 2009 Nov 17] [cited 2014 Mar. 29].

- [24] Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
- [25] Zairis MN, Tsiaousis GZ, Patsourakos NG, Georgilas AT, Kontos CF, Adamopoulou EN, et al. The impact of treatment with omeprazole on the effectiveness of clopidogrel drug therapy during the first year after successful coronary stenting. *Can J Cardiol* 2010;26:e54-7
- [26] Zuern CS, Geisler T, Lutlsky N, Winter S, Schwab M, Gawaz M. Effect of comedication with proton pump inhibitors (PPIs) on post-interventional residual platelet aggregation in patients undergoing coronary stenting treated by dual antiplatelet therapy. *Thromb Res* 2010;125:e51-4.
- [27] Hokimoto S., et al., (2014). Impact of CYP2C19 polymorphism and proton pump inhibitors on platelet reactivity to clopidogrel and clinical outcomes following stent implantation. *Thromb Res.* 2014 Apr;133(4):599-605. doi: 10.1016/j.thromres.2014.01.003. Epub 2014 Jan 9.
- [28] Kashour T., et al., (2014). Changing prescription pattern of omeprazole among patients receiving clopidogrel. *Int Heart J.* 2014;55(2):93-5. Epub 2014 Mar 14.
- [29] Funck-Brentano C., et al. (2013). Effects of rabeprazole on the antiplatelet effects and pharmacokinetics of clopidogrel in healthy volunteers. *Arch Cardiovasc Dis.* 2013 Dec;106(12):661-71. doi: 10.1016/j.acvd.2013.09.002. Epub 2013 Nov 15.