Original Article

The Prevalence of Coadministration of Clopidogrel and Proton Pump Inhibitors

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ABSTRACT

Introduction: Clopidogrel is mainly indicated for the prevention of vascular ischaemic events in patients with symptomatic atherosclerosis, non-ST elevation acute coronary syndrome and as an adjuvant to reperfusion therapy for ST segment elevation myocardial infarction (MI) [with aspirin]. This study to determine the prevalence of co-administration of clopidogrel and proton pump inhibitors (PPI) in one year prescription data of 791 aged-care residents.

Methods: One year prescription records of 791 aged-care residents was analysed for prevalence of co-prescribing of clopidogrel and PPIs, and aspirin with clopidogrel and PPIs. Prevalence of co-prescribing of clopidogrel, aspirin and PPI in diabetic patients and clopidogrel with various CYP2C19 inhibitors was also determined.

Results: Of the 791 residents 60 were prescribed clopidogrel, 248 were on aspirin, and 326 were prescribed a PPI. Among residents who were prescribed PPIs, 155 were on omeprazole, 72 on pantoprazole, 15 on lansoprazole, 44 on esomeprazole and 51 on rabeprazole. Eleven of these residents had taken more than one PPI during that time. Thirty nine residents took a combination of clopidogrel and a PPI (any PPI) for a mean 202 days (SD 12). Thirteen residents were on the combination of aspirin and clopidogrel for a mean of 202 days (SD 111). Nine residents took the combination of clopidogrel, aspirin and a PPI (any PPI) for a mean of 173 days (SD 81).

Conclusion: A clinically significant number of residents in this cohort were taking the combination of clopidogrel and a PPI. The majority of residents who were on PPI were taking omeprazole. Residents who were on the combination of clopidogrel and a PPI with or without aspirin were on these combinations for a significantly long duration.

Key words: Clopidogrel, PPI Aspirin.

INTRODUCTION

Clopidogrel is mainly indicated for the prevention of vascular ischaemic events in patients with symptomatic atherosclerosis, non-ST elevation acute coronary syndrome (ACS) [with aspirin] and as an adjuvant to reperfusion therapy for ST segment elevation myocardial infarction (MI) [with aspirin].[1] Proton pump inhibitors (PPI) are generally prescribed to patients taking aspirin and clopidogrel as a prophylactic measure to prevent GI tract bleeding. Recent studies have suggested that PPIs inhibit the antiplatelet activity of clopidogrel increasing the risk of major cardiovascular events in patients taking clopidogrel and PPIs together following an ACS.[1-3]

Clopidogrel is a prodrug activated in the liver to an active thiol metabolite that is specific and irreversible inhibitor of platelet $P2Y_{12}$ ADP receptor.[4] This bioactivation is mediated by hepatic cytochrome P450 isoenzymes, with cytochrome P450 2C19 (CYP2C19) and cytochrome P450 3A4 (CYP3A4) playing major role.[3] The genes encoding CYP2C19 are polymorphic and patients with reduced function CYP2C19 allele

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have lower levels of active metabolite of clopidogrel such that carriers of this allele were twice as likely to die from MI or stroke, as compared with non-carriers and an increase in risk of stent thrombosis by 3 times due to diminished platelet inhibition relative to those without such polymorphisms.[4-6] Proton pump inhibitors are also metabolized by CYP2C19 in varying degrees.[7] Evidence suggests that some PPIs can inhibit CYP2C19 and hence inhibit clopidogrel's.

Biological activation: The randomized, double blind OCLA (Omeprazole Clopidogrel Aspirin) study[2] showed that omeprazole significantly decreased clopidogrel inhibitory effect on platelet P2Y12 as assessed by the vasodilator-stimulated phosphoprotein (VASP). The finding of this study was consistent with a previous observational study which showed that patients using PPIs with the combination of clopidogrel and aspirin had significantly higher VASP values than nonusers of PPIs.[8] VASP phosphorylation in human platelets correlates with platelet inhibition and there is direct link between VASP and major adverse cardiac events (MACE).[9]

A retrospective cohort study in patients taking clopidogrel with or without a PPI after hospitalization for ACS reported that use of clopidogrel plus a PPI was associated with an increased risk of death or rehospitalisation for ACS compared with use of clopidogrel without a PPI.[10] Approximately 60% of patients that took a PPI medication in this study were prescribed omeprazole.

A population based nested case-control study in 13636 patients (734 cases and 2057 controls) reported that in patients taking clopidogrel following an acute MI, concurrent use of PPI was associated with increased risk of reinfarction (OR 1.27, 95% CI 1.03-1.57.[3] They found no association with more distant exposure to PPI. Pantoprazole which does not inhibit cytochrome P450 2C19 and was shown to have no association with readmission for MI.

In contrast to the reported negative omeprazole-clopidogrel drug interaction, a mechanistic study[2] conducted in 300 coronary artery disease (CAD) patients undergoing PCI implicated that intake of pantoprazole or esomeprazole was not associated with impaired response to clopidogrel as assessed by VASP assay and aggregometry. Similarly a pharmacokinetic study in healthy subjects showed that lansoprazole did not alter the antiplatelet activity of clopidogrel measured as inhibition of platelet aggregation (IPA).[11]

However CYP2C19 does not appear to be a major metabolic pathway for clopidogrel metabolism with evidence suggesting that CYP3A4 is a major contributor of clopidogrel active metabolite generation. Lau et al reported that atorvastatin reduces platelet inhibition by clopidogrel due to competitive inhibition of CYP3A4 substrate in a dose dependant manner.[12] CYP3A4 stimulators rifampin and St. John's Wort enhanced platelet inhibition by clopidogrel, whereas agents that competed with clopidogrel for CYP3A4 (e.g. erythromycin) attenuated platelet inhibition.

We studied the prevalence of co-prescription of PPI with clopidogrel and aspirin in one year prescription data of 791 aged-care residents.

METHODS

Study was approved by the Curtin University Human Research Ethics Committee. We studied the prescription records of 791 aged-care residents for the prevalence of co-prescribing of clopidogrel and PPIs, and aspirin with clopidogrel and PPIs. The data file consisted of 65259 records of drugs prescribed over the course of a year (from 02-01-2007 to 31-12-2007). We also studied the prevalence of co-prescribing of clopidogrel with various CYP 2C19 inhibitors. The prevalence of co-prescribing of aspirin, clopidogrel and PPIs in diabetic residents was also determined. Diabetics are at high risk of cardiovascular disease and more likely to be on this combination.

PPIs included in the analysis were omeprazole, pantoprazole, lansoprazole, esomeprazole, and rabeprazole. The CYP2C19 inhibitors included were cimetidine, efavirenz, fluoxetine, fluvoxamine, indomethacin, ketoconazole, modafinil, oxcarbazepine, ticlopidine, topiramate and voriconazole. We classified residents as diabetic if they were taking any of the following anti-diabetic drugs, namely, insulin, metformin, glibenclamide, gliclazide, glimepiride, glipizide, pioglitazone, rosiglitazone, acarbose, and ripaglinide at any time during the study period.

The data file consisted of all prescribed medicines for the selected residents provided by Webstercare during 2007. It consisted of the following fields: residents' date of birth, gender, drug name, dose, dispensed date, date of commencement and the last date of taking the drug. Each patient was assigned with a unique code number. A person-based analysis was performed. Each person having the various available combinations of drugs and

the duration for which they had been on the combination therapy were determined. This was to ascertain that the patients used the combination of drugs concurrently and not at different periods. The number of days a patient was on a drug or combination of drugs was worked out by dividing quantity of drug dispensed by dose per day.

Case reports in Australia on cardiovascular events due to the combination of clopidogrel and PPI; and aspirin, clopidogrel and PPI were obtained from ADRAC (Adverse Drug Reactions Advisory Committee).

Statistical analysis: The data file was provided as a Microsoft Excel© spreadsheet but was transferred into DBF format for statistical analysis. SAS statistical software program[13] was used to obtain tables of the mean, standard deviations and median number of days when the different combinations of drugs were taken. The DOS-based CLIPPER database program was used to calculate all the details like searching for the drug frequencies, identifying dates where each type of drug was taken, and from that the number of days where each combination of drugs are taken.

RESULTS

The data file consisted of records of 791 selected aged-care residents with a mean age of 90 years (SD 12.1); 585 female residents with a mean age of 91 years (SD 11.1) and 206 male residents with a mean age of 87 years (SD 12.5) (Table 1).

Table 1: Residents' demographics

	No. of residents	Mean age (years)	SD
Total	791	90.3	12.1
Female	585	91.1	11.1
Male	206	88.2	12.5

Of 791 residents 60 were prescribed clopidogrel, 248 were prescribed aspirin, and 326 were prescribed PPI (any PPI) (Table 2). Among residents who were on PPI, 155 were on omeprazole, 72 on pantoprazole, 15 on lansoprazole, 44 on esomeprazole and 51 on rabeprazole. Eleven of these residents had taken more than one PPI during the study period.

Thirty nine residents took a combination of clopidogrel and a PPI (any PPI) for mean 202.9 days (SD 11.5). Of the 39 people on clopidogrel and a PPI, 18 residents were on omeprazole, 9 rabeprazole, 7 esomeprazole, 6 pantoprazole and 1 on lansoprazole (Table 3).

Table 2: Number of residents on various drugs

Drugs	No. of residents (n)
Clopidogrel	60
Aspirin	248
PPI (any PPI)	326
Omeprazole	155
Pantoprazole	72
Lansoprazole	15
Esomeprazole	44
Rabeprazole	51

Table 3: Combination of clopidogrel with PPIs

Drugs	No. of residents	Mean number of days	SD
Clopidogrel with			
PPI(any PPI)	39	202.9	11.5
Omeprazole	18	182.1	137.3
Pantoprazole	6	185.3	88.4
Lansoprazole	1	62.0	-
Esomeprazole	7	283.5	41.2
Rabeprazole	9	172.6	103.4

Thirteen residents were on combination of aspirin and clopidogrel for the mean of 202.3 days (SD 111.1). Nine residents took the combination of clopidogrel, aspirin and a PPI (any PPI) for mean 203.1 days (SD 81). Among patients taking aspirin, clopidogrel and PPI, 6 were on omeprazole for mean 222.2days (SD 77) and 3 patients were on rabeprazole for mean 165 days (SD 90.6) (Table 4).

Table 4: Combination of clopidogrel and aspirin with PPIs

Drugs	No. of patients	Mean no. of days	SD
Clopidogrel and aspirin	13	202.3	111.1
PPI(any PPI)	9	203.1	81.0
Omeprazole	6	222.2	76.9
Rabeprazole	3	165.0	90.6

Among other CYP2C19 inhibitors, only one resident took a combination of fluoxetine and clopidogrel for 29 days. Five diabetic patients were on the combination of clopidogrel and a PPI (any PPI) for the mean of 206.4 days (SD 105.8) with 3 residents on pantoprazole, 1 on omeprazole and 1 resident on esomeprazole (Table 5). Only one diabetic resident in this cohort was taking combination of aspirin, clopidogrel and omeprazole for 151 days (Table 6).

Table 5: Combination of clopidogrel and PPI by diabetes status of residents

Diabetic status	Drugs	No. of residents	Mean no. of days	SD
	Clopidogrel with			
Non-diabetic	PPI(any PPI)	34	202.3	113.8
	Omeprazole	17	184.9	130.6
	Pantoprazole	3	177.6	78.7
	Lansoprazole	1	62.0	-
	Esomeprazole	6	277.6	41.8
	Rabeprazole	9	172.6	103.4
Diabetic	PPI(any PPI)	5	206.4	105.8
	Omeprazole	1	134.0	-
	Pantoprazole	3	193.0	114.8
	Lansoprazole	0	-	-
	Esomeprazole	1	319.0	-
	Rabeprazole	0	-	-

Table 6: Combination of clopidogrel and aspirin with PPI by diabetes status of residents

Diabetic status	Drugs	No. of residents	Mean no of days	SD
	Clopidogrel and aspirin with			
Non-diabetic	PPI(any PPI)	8	209.6	84.1
	Omeprazole	5	236.4	76.7
	Rabeprazole	3	165.0	90.6
Diabetic	PPI (omeprazole)	1	151.0	-

One case report on adverse cardiac vascular event was obtained from ADRAC regarding the combination of aspirin, clopidogrel and PPI. The case was reported on December 2008 and involved a 76 year old male patient who was in combination of aspirin, clopidogrel and omeprazole. He suffered bradycardia and coronary artery occlusion reported as result of drugs being ineffective.

DISCUSSION

Clopidogrel is one of the highest selling drugs in the world. In 2003, 1.3 million PBS prescriptions for clopidogrel were dispensed in Australia.[14] Clopidogrel supply increased rapidly in Australia since its introduction, from 1.2 to 9.0 defined daily doses DDD/1000 population/day. The defined daily dose (DDD)/ thousand population/day shows how many people, in every thousand patients, are taking the standard dose of a drug every day. Between 30% and 73% of clopidogrel supply was accounted for by people receiving cardiac stents.[15] Proton pump inhibitors are also one of the most frequently prescribed classes of drug in the world with expenditure of approximately 14.3 billion US dollars globally in the year 2006 alone.[16] 4.42 million PBS prescriptions for esomeprazole and 3.88 million prescription for omeprazole were dispensed in Australia in the year 2006-07 making them third and fourth most prescribed subsidised drugs in that year respectively.[17] Recent guidelines from the American Heart Association, the American College of Gastroenterology, and the American College of Cardiology recommend a PPI for many patients receiving aspirin following a heart attack.[18] Clopidogrel and aspirin are often prescribed together for patients treated either medically or with percutaneous coronary intervention (PCI) following a heart attack. It is probable that millions of patients worldwide will take the combination of clopidogrel and a PPI. However there are no guideline recommendations for using prophylactic PPIs with clopidogrel for reducing GI bleeding. Considering the widespread use of these medications, it becomes important to further research the interaction between these drugs.

A significant association was reported between clopidogrel and PPI suggesting that their concomitant use may lead to attenuation of the benefits of clopidogrel leading to adverse cardiac outcomes.[10] A randomized controlled trial showed that omeprazole significantly decreased clopidogrel inhibitory effect on platelet P2Y.[12]

Depending on the exposure to these drugs following a heart attack, it was estimated that 5-15% of early readmissions for MI among patients taking clopidogrel could be the result of this drug interaction.[3] Studies show that longer duration of treatment with clopidogrel plus PPI was associated with adverse outcomes.[3,10] Our study showed that residents, who were on combination of clopidogrel and PPI, with or without aspirin, were on these combinations for a significantly long duration (mean of 202 days a year).

It is also important to assess if inhibition of clopidogrel action by PPIs is a drug effect or class effect. The reported negative effects of omeprazole on clopidogrel function was not seen in patients treated with pantoprazole, esomeprazole and lansoprazole.[7,11] However there was no study done to directly compare the effects of different PPIs on clopidogrel function. Evidence suggests that omeprazole is most likely to decreases anti-platelet activity of clopidogrel possibly due to inhibition of

the CYP2C19 enzyme.[2,3,10] In our study 155 out of 326 (47%) patients who were taking PPI were on omeprazole. The only case report available from ADRAC involved omeprazole. Omeprazole was the first generic PPI, introduced in 2002, and still comprises majority of prescriptions for PPIs since its introduction.[16] So it is important to determine that the adverse outcomes reported with omeprazole are not because of its widespread use as compared to other PPIs.

Several studies have demonstrated that CYP2C19 gene polymorphism is associated with greater clopidogrel non-response and an increased risk of adverse cardiovascular events.[4,6] Some studies showed that as many as 30% of people worldwide are born with this particular genetic variation.[6] The way PPIs interfere with the conversion of clopidogrel to an active form may mimic this genetic variation that produces lower amounts of the enzyme. So influence of PPI in low clopidogrel responder group may be high resulting in high risk of adverse effects of this combination. Likewise, the influence of PPIs may also be important in patients receiving atorvastatin. As both atorvastatin and PPIs have been shown to inhibit clopidogrel activity via different metabolic pathways, this combination may potentiate significant drug-drug interactions with clopidogrel. Taking this genetic variation into account, Bonillo et al.suggested that adjusting the clopidogrel dose individually in patients according to their VASP index, before PCI, in daily clinical practice improved the clinical outcome after coronary stenting. This type of personalized medicine might also help in determining genetic status of individual patients, if one is a high responder or low responder to clopidogrel, and allow adjustment of treatment accordingly.[9]

The US Food and Drug Administration have released an early communication about a safety review of potential interaction between clopidogrel and PPIs.[19] The FDA highlighted the need for additional studies to evaluate the effectiveness of clopidogrel when used concurrently with PPIs. Until further information is available FDA recommended the following.[19]

Healthcare providers should continue to prescribe and patients should continue to take clopidogrel as directed, because clopidogrel has demonstrated benefits in preventing blood clots that could lead to a heart attack or stroke.

Healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI in patients taking clopidogrel.

Patients taking clopidogrel should consult with their healthcare provider if they are currently taking or considering taking a PPI .

CONCLUSION

A clinically significant number of residents were taking the combination of clopidogrel and a PPI. Almost 50% of the residents who were on PPI were prescribed omeprazole. Residents on the combination of clopidogrel and a PPI, with or without aspirin, were on these combinations for a significantly long duration. Aspirin-clopidogrel antiplatelet dual therapy is widely prescribed worldwide, with PPIs frequently prescribed to prevent GI bleeding. Recent studies have suggested that PPI could inhibit clopidogrel's antiplatelet action leading to increased risk of adverse cardiovascular events in patients. Among the PPIs, omeprazole is reported as most likely to decrease anti-platelet activity of clopidogrel. The clinical impact of these results must be assessed by further studies comparing cardiovascular outcomes for patients taking clopidogrel plus PPI vs. clopidogrel without PPI, and comparing the impact of different PPIs on the effectiveness of clopidogrel.

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