The prevalence of co-administration of clopidogrel and proton pump inhibitors

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What do we know?

- 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.
- Clopidogrel is metabolised by hepatic cytochrome P450 2C19 to an active thiol metabolite that is specific and irreversible inhibitor of platelet $P2Y_{12}$ ADP receptor and inhibits platelet aggregation.
- Evidence suggests that some PPIs (mainly omeprazole) can inhibit CYP 2C19 and hence inhibit the bioactivation of clopidogrel.

What this study adds?

- This study shows the prevalence of co-administration of clopidogrel with any PPIs in a cohort of aged cared residents in Western Australia.
- A clinically significant number of aged-care residents in this cohort were taking the combination of clopidogrel and a PPI with almost 50% of the residents on a combination of clopidogrel with omeprazole.
- Given the potential interaction between clopidogrel and PPIs, it is necessary to review the co-administration of clopidogrel with PPIs (especially omeprazole and esomeprazole) to prevent an adverse outcome in this group of patients.

Abstract

Background: Recent studies have suggested that proton pump inhibitors (PPIs) inhibit the antiplatelet activity of clopidogrel increasing the risk of major cardiovascular events in patients taking clopidogrel and PPIs together.

Aim: This study aims to determine the prevalence of co-administration of clopidogrel and proton pump inhibitors (PPIs) amongst residents of aged-care facilities in Western Australia.

Methods: One year prescription records of 791 aged-care residents were 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 examined.

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 prescribed omeprazole, 72 pantoprazole, 15 lansoprazole, 44 esomeprazole and 51 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 a mean 203 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). Only one patient on clopidogrel was receiving a CYP2C19 inhibitor in addition to a PPI.

Conclusions: A clinically significant number of residents in this cohort were taking the combination of clopidogrel and a PPI, mainly 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 which could increase the risk of adverse cardiovascular events.

Keywords: Clopidogrel, proton pump inhibitors, interaction, acute coronary syndrome, cardiovascular disease

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 (PPIs) 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. This increases 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 and inhibits platelet aggregation [4]. This bioactivation is mediated by hepatic cytochrome P450 isoenzymes, with cytochrome P450 2C19 (CYP2C19) and cytochrome P450 3A4 (CYP3A4) playing major roles [3]. The genes encoding CYP2C19 are polymorphic and patients with reduced function CYP2C19 allele have lower levels of active metabolite of clopidogrel. The carriers of this allele were twice as likely to die from MI or stroke, as compared with non-carriers and have a three times increase in risk of stent thrombosis 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 the bioactivation of clopidogrel [2]. The randomized, double blind OCLA (Omeprazole Clopidogrel Aspirin) study [2] showed that omeprazole significantly decreased clopidogrel inhibitory effect on platelet $P2Y_{12}$ 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 aggregation and there is direct link between VASP and major adverse cardiac events [9].

A retrospective cohort study in patients taking clopidogrel with or without a PPI after hospitalization for ACS reported that use of clopidogrel with 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]. Pantoprazole which does not inhibit CYP2C19 was shown to have no association with readmission for MI.

In contrast to the reported negative omeprazole-clopidogrel drug interaction, a mechanistic study [7] conducted in 300 coronary artery disease (CAD) patients undergoing PCI indicated 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 compete with clopidogrel for CYP3A4 (e.g. erythromycin) attenuated platelet inhibition.

Methods

The 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 CYP2C19 inhibitors. The prevalence of co-prescribing of aspirin, clopidogrel and PPIs in diabetic residents was also determined as diabetics are at high risk of cardiovascular disease and more likely to be on this combination.

PPIs included in 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 on 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 random sample of aged care residents provided by Webstercare during 2007. It consisted of 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 calculated by dividing quantity of drug dispensed by dose per day.

The data file was provided as a Microsoft Excel® spreadsheet but was transferred into DBF format for statistical analysis. SAS statistical software program 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 drug frequencies and identify the dates when each type of drug was taken, and from that the number of days for each combination of drugs taken.

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

Results

The data file consisted of records of 791 selected aged-care residents with a mean age of 90 years (SD 12.1). There were 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) [Table1].

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 were on the 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 on rabeprazole, 7 on esomeprazole, 6 on pantoprazole and 1 on lansoprazole [Table 3].

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].

The co-administration of clopidogrel with another CYP2C19 inhibitor was only observed in one resident who 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 on esomeprazole [Table 5]. Only 1 diabetic resident in this cohort was taking combination of aspirin, clopidogrel and omeprazole for 151 days [Table 6].

One case report on adverse cardiovascular event was obtained from ADRAC regarding the combination of aspirin, clopidogrel and PPI. The case was reported in December 2008 and involved a 76 year old male patient who was on the combination of aspirin,

clopidogrel and omeprazole. He suffered bradycardia and coronary artery occlusion reported as result of the 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 [13]. Clopidogrel supply has increased rapidly in Australia since its introduction, from 1.2 to 9.0 defined daily doses (DDD)/1000 population/day. The 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 [14]. 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 [15]. In Australia 4.42 million PBS prescriptions for esomeprazole and 3.88 million prescription for omeprazole were dispensed in the year 2006-07 making them third and fourth most prescribed subsidised drugs in that year respectively [16]. 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 [17]. Clopidogrel and aspirin are often prescribed together for patients treated either medically or with percutaneous coronary intervention (PCI) following a heart attack. It is likely that millions of patients worldwide will take the combination of clopidogrel and a PPI. 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 PPIs 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 $P2Y_{12}$ ADP receptor. 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 [15]. The adverse outcomes reported with omeprazole could be associated with its widespread use 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. Individual with this polymorphism can be at an increased risk of thrombosis and this risk is further aggravated if they take a combination of clopidogrel with PPIs. Taking this genetic variation into account, Bonillo et al. [9] showed 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 patient, if one is a high responder or low responder to clopidogrel, and allow adjustment of treatment accordingly.

The US Food and Drug Administration have released a communication about the safety review of potential interaction between clopidogrel and PPIs [18]. 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 issue the following advice [18]:

- Avoid using omeprazole and clopidogrel together and at any time of the day.
- Avoid using other potent CYP 2C19 inhibitors, including esomeprazole, with clopidogrel.
- FDA does not have enough evidence to preclude the use of other PPIs other than omeprazole and esomeprazole.
- Patients taking clopidogrel should consult with their healthcare provider if they are currently taking or considering taking a PPI.
- Patients who use clopidogrel and need a medication to reduce stomach acid can use antacids, ranitidine, famotidine, nizatidine but not cimetidine.

A clinically significant number of aged-care residents in this cohort 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, which significantly increase the risk of adverse cardiac events. This drug interaction is now evident and it is necessary to review the co-administration of clopidogrel with PPIs (especially omeprazole and esomeprazole) in this group to prevent an adverse outcome. The clinical impact of these results must be assessed by further studies comparing cardiovascular outcomes for patients taking clopidogrel plus PPI versus clopidogrel without PPI, and comparing the impact of different PPIs on the effectiveness of clopidogrel.

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Conflicts of interest

None

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Table 1. Residents' demographics

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

Table 2. Number of residents on various drugs

Drugs	No. of residents	(%)
Clopidogrel	60	7.6
Aspirin	248	31.4
PPI (any PPI)	326	41.2
Omeprazole	155	19.6
Pantoprazole	72	9.1
Lansoprazole	15	1.9
Esomeprazole	44	5.6
Rabeprazole	51	6.4

Table 3. Combination of clopidogrel with PPIs

Drugs	No. of residents (n)	Mean no. 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

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
Clopidogrel and aspirin with			
PPI(any PPI)	9	203.1	81.0
Omeprazole	6	222.2	76.9
Rabeprazole	3	165.0	90.6

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

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