Impact of Calcium Channel Blockers on Aspirin Reactivity in Patients With Coronary Artery Disease

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Abstract

Purpose: Calcium channel blockers (CCBs) do not reduce the risk of initial or recurrent myocardial infarction (MI) in patients diagnosed with stable coronary artery disease (CAD). The aim of this current study was to evaluate the association between CCBs and aspirin resistance in patients with CAD.

Methods: Patients with stable CAD who were regularly taking aspirin (75-100 mg qd) for at least one month prior to enrollment in the study were included. The VerifyNow system was used for platelet function testing with high on-aspirin platelet reactivity (HAPR) defined as aspirin reaction units (ARU) >550. We compared patients treated with CCBs versus control group.

Results: 503 patients with CAD were included in this study, 88 were treated with CCBs; Mean age (67.9 ± 9.7 in the CCB group vs 66.5 ± 11.4 in the control group, $p=0.288$), gender (77.3 male vs. 82.9%, $p=0.214$) and rates of diabetes mellitus (34.7 vs. 36.9%, $p=.121$) were similar. Rates of hypertension were higher in the CCB group (83.9 vs. 63.5%, $p<0.01$), but rates of past MI were lower (47.1 vs. 59.7%, $p=0.039$). The mean ARU was 465.4 ± 70.0 for patients treated with CCBs versus 445.2 ± 60.0 in controls ($p=0.006$). Similarly, 15.9% of CCB patients demonstrated HAPR compared to 7.0% ($p=0.006$). In a multivariate analysis, the administration of CCBs was independently associated with HAPR (OR- 1.72, 95% CI 1.04 – 8.91, $p=0.047$).

Conclusions: Usage of CCBs is positively correlated with aspirin resistance. These findings may suggest an adverse pharmacologic effect of CCBs among patients with stable CAD treated with aspirin.

Introduction

In platelets, one of the pivotal activating factors that leads to aggregation occurs through the messaging cascade initiated by calcium influx [1]. Initially, agonists like subendothelial collagen, thromboxane A₂ (TXA₂), and ADP released from platelets all contribute to an intracellular increase in calcium storage. As the calcium concentration rises within the cell, the signaling cascade leads to both actin cytoskeleton reorganization and degranulation, which are essential for platelet aggregation [1–3]. Aspirin prevents these steps and halts platelet aggregation. It inhibits the activation of arachidonic acid, thereby preventing TXA₂ from causing a rise in intracellular calcium [4]. However, the effects of aspirin are dependent on many factors. Nearly a quarter of patients who have been prescribed aspirin for prevention of cardiac or cerebral vascular events have an inadequate response to the drug [5,6]. This decreased response may stem from many sources, including increased levels of epinephrine, which can inhibit aspirin's effectiveness and reverse its anti-thrombotic effect [7,8]. Similarly, increased levels of homocysteine in the plasma are associated with augmented aspirin resistance among patients with coronary artery disease (CAD) [9,10]. Aspirin resistance can be assessed using quantitative measures, including aspirin reaction units (ARU) and high on-aspirin platelet reactivity (HAPR). Importantly, previous studies have demonstrated that patients with increased HAPR have increased risk of experiencing recurrent ischemic events [11,12].

In patients with stable CAD, calcium channel blockers (CCBs) are often co-administered with aspirin to treat hypertension and to alleviate angina pectoris. However, in patients with acute coronary syndrome, CCBs have not been shown to reduce the risk of initial or recurrent cardiovascular events [13–15]. It is not currently understood why CCBs, which are able to treat hypertension and promote coronary vasodilation, have not been shown to reduce the risk of coronary adverse events and/or mortality. We hypothesize that one of the mechanisms underlying their inability to do so relies on the pharmacological interaction between CCBs and aspirin (e.g. [HAPR]). In this study, we have examined the response to aspirin in patients with stable CAD who either use or do not use CCBs to verify whether an adverse interaction exists between aspirin's effectiveness and the usage of CCBs.

Methods

Study population

This single-center observational study included an analysis of prospectively enrolled patients throughout January 2012 to June 2019 at one of the two campuses of the Rabin Medical Center, a tertiary hospital. Patients were either evaluated in the outpatient clinic (e.g. routine follow-up) or admitted at our hospital, for evaluation of angina symptoms. All patients had stable CAD at presentation, and have undergone coronary angiography 3 months or more prior to recruitment, demonstrating significant CAD (defined as a stenosis of at least 50% in one or more epicardial coronary arteries by coronary angiography). All patients were regularly taking aspirin (75-100 mg qd) for at least one month prior to enrolment into the current study. Exclusion criteria were as follows: acute coronary syndrome at the time of platelet function testing, known malignant disease (patients with remission >2 year were eligible), sepsis or acute infection, active inflammatory/rheumatic disease, major surgery in the last 6 months (coronary artery bypass graft within the last 3 months), chronic liver failure, treatment with oral anticoagulation, allergy to- or non-adherence with aspirin and thrombocytopenia (<100K/micl). The institutional review board approved the study, which was performed in accordance with ethical principles portrayed in the Helsinki declaration.

Reagents and Devices

Following informed consent and patients' verbal confirmation of adherence with aspirin within the last month including the day of the test, blood was drawn from the antecubital vein and sent to the platelet function test (VerifyNow). The VerifyNow system (Accumetrics, San Diego, CA) is a whole-blood assay based on light transmission measurements. The aspirin-specific cartridge, used in the current study, is designed and applied to assess platelet dysfunction caused by aspirin (the effect of aspirin on platelets). In the aspirin-specific assay, arachidonic acid activates platelets, and the activated platelets bind to fibrinogen-coated beads to form an aggregate. The degree of aggregation is quantified by a corresponding increase in light transmission and is reported in ARU. HAPR was defined as ARU >550 in consistency with previous studies [16,17].

Data sources and classifications

Data were obtained from the hospital's computerized medical records and included demographic and clinical characteristics, cardiovascular risk factors and co-morbidities, procedural characteristics and workup (e.g., blood tests, echocardiography). Glomerular filtration rate was calculated by the Modification of Diet in Renal Disease formula. Chronic kidney disease was defined as glomerular filtration rate below 50 mL/min/1.73 m². Anemia was defined as hemoglobin levels lower than 13.0 g/dL for men and 12.0 g/dL for women.

Statistical analysis

Patient characteristics were presented as mean and standard deviation (SD) for continuous variables and percent for the categorical data. Chi-square or Fischer exact tests were used for analysis of categorical variables when appropriate. The unpaired student t-test or analysis of variance (ANOVA) were used for analysis of continuous variables. This was used to compare HAPR according to treatment with CCBs or not and the rates of HAPR according to each type of CCBs. A multivariate analysis study was performed using binary hierarchical logistic regression, to assess the independent factors associated with HAPR. Statistical analysis was performed using IBM SPSS Statistics 27 software. For each test, P< 0.05 was considered as statistically significant.

Results

Overall, 503 patients were included in this study. There were 88 patients who had received CCBs – Amlodipine (n=41), Lercanidipine (n=33), Nifedipine (n=8) and Diltiazem (n=6). Mean age was 67.99.7 years for those treated with CCBs versus 66.511.4 years for the control group (p=0.288), 77.3% were male vs. 82.9% (p =0.214) and 34.7 vs. 36.9% had diabetes mellitus (p =0.121). Differences were observed in the rates of past history of hypertension (83.9% in the CCB group vs. 63.5% in the control group, p<0.01), rates of past MI (47.1% vs. 59.7%, p=0.031) and past PCI (52.9% vs. 64.0%, p = 0.039, table 1).

In patients taking CCBs, HAPR was observed in 7.0% in the CCB group and 15.9% in the control group (p =0.006, table 2, figure 1). Similarly, the mean ARU was 465.470.0 in the CCB group, compared to 445.260.0 for the control group (p=0.006, figure 2). There were 7 patients with HAPR who were treated with Amlodipine (17.1%), 5 patients with Lercanidipine (15.2%), 1 with Nifedipine (12.5%) and 1 with Diltiazem (16.7%, p=0.825 for differences between the CCBs).

In a binary logistic regression model, adjusted for sex, age, BMI, hypertension, hyperlipidemia, chronic kidney disease, diabetes mellitus type II, smoking history, past myocardial infarction, and type of CCB, patients taking CCBs were 1.72 times more likely to have HAPR compared to those not taking CCBs (95% CI of 1.04 – 8.91, p = 0.047). A second factor associated with increased risk of HAPR was diabetes mellitus (OR = 2.25, 95% CI 1.25-4.17, p = 0.039) (table 3). The type of CCB (Amlodipine, Lercanidipine, Nifedipine or Diltiazem) showed no clear correlation with HAPR (p = 0.427). There were also no differences in rates of HAPR when classified according to dihydropyridine or non- dihydropyridine, nor according to P-gp inhibiting or non- P-gp inhibiting CCBs.

Discussion

The results of this study demonstrate a significant association between treatment of CCBs and aspirin responsiveness for patients with stable CAD. In these patients, the concomitant use of CCBs had a weakening effect on the pharmacologic potency of aspirin. Our study did not find an association between the type of CCB used and HAPR.

Our results are consistent with similar studies performed by Gremmel et al. which demonstrated that CCBs are associated with a decreased platelet response to clopidogrel [18,19]. In these studies, tests were performed via flow cytometry and the VerifyNow system to conclude that the addition of CCBs to clopidogrel leads to a reduced antiplatelet response compared to clopidogrel alone. Potential mechanisms include the inhibition of cytochrome 3A4 and the inhibition of P-glycoprotein (P-gp) by CCBs [18,19]. The first mechanism is based on clopidogrel as a prodrug that requires the activity of cytochrome 3A4 for its active form. If cytochrome 3A4 is inhibited by CCBs, clopidogrel cannot be appropriately metabolized and its effect is diminished [18–22]. The latter mechanism considers that several CCBs inhibit the effect of P-gp, which is a necessary protein for clopidogrel's intestinal absorption [19,23].

Our hypothesis is based on similar explanations for how CCBs attenuate aspirin's effect, as evidenced by the increased rate of HAPR. The P-gp theory could be one of the mechanisms that accounts for our results. While some studies have concluded that aspirin is not a substrate for P-gp [24], others have found that P-gp causes efflux of aspirin [25] and is therefore associated with P-gp-based absorption in the gut. Hence, the concomitant use of CCBs with aspirin may lead to decreased bioavailability of the anti-thrombotic drug. In our study, the P-gp inhibiting CCBs that were used included Nifedipine and Diltiazem. The association we found with increased HAPR was with use of CCBs overall, irrespective of the type of CCB; we estimate therefore that the P-gp theory accounts for only part of this association.

Another mechanism that could explain the increased HAPR with usage of CCBs is based on the Etingen study that demonstrated how CCBs enhance cholesterol ester (CE) hydrolysis [26]. The liver is the site for both CE and aspirin hydrolysis, with CE hydrolyzed into cholesterol and aspirin hydrolyzed into salicylic acid [27,28]. When aspirin is hydrolyzed into salicylic acid, its antiplatelet activity is transformed to anti-inflammatory activity [29]. It is therefore also possible that CCBs upregulate the hydrolysis of aspirin in a similar fashion to the hydrolysis of cholesterol esters. The increased formation of salicylic acid depletes the aspirin load and leads to an increase in HAPR.

Finally, one of the mechanisms of action of aspirin is through the inhibition of prostaglandin (PG) H₂ synthase (cyclooxygenase), preventing the generation of prostaglandin G₂ and prostaglandin H₂, and ultimately TXA₂ [4]. For these events to occur, PGH₂ synthase requires arachidonic acid liberation from phospholipids. However, arachidonic acid is released from phospholipids only once calcium levels rise within the cell. If calcium levels fail to rise due to the presence of calcium-blocking agents, aspirin may have a diminished ability to exert its anti-platelet effects [4,7,30]. In this scenario, CCBs hamper the antiplatelet effects of aspirin by limiting its potential to prevent TXA₂ formation. It is therefore

presumable that dihydropyridine and non-dihydropyridine should share similar effectivities on HAPR due to arachidonic acid presence in both smooth and cardiac muscle [31]. Dihydropyridines primarily act on smooth muscle whereas non-dihydropyridines primarily act on cardiac muscle; their influences would each cause an independent decrease in TXA2 formation.

In our study, the non-dihydropyridine CCB (Diltiazem) did not show an independent association with HAPR as compared to the dihydropyridine CCBs (Amlodipine, Lercanidipine, and Nifedipine). Similarly, both P-gp inhibiting (Nifedipine and Diltiazem) and non-P-gp inhibiting CCBs (Amlodipine and Lercanidipine) were used. However, we did not identify an association between the type of CCB and HAPR. Future studies, which compare larger number of patients receiving CCBs, may re-assess such associations between the type of CCBs and aspirin response.

While observational, our results are the first to examine the association between CCBs and HAPR, and may suggest a mechanism for the lack of prognostic benefit in patients with ischemic heart disease treated with CCBs [13–15]. Understanding this mechanism may allow for a more personalized assessment of how to maximize cardio-protection for patients with cardiovascular risk factors. Further research is needed in order to determine the translational impact of this observation, and to guide the medical management of patients with stable CAD treated with antiplatelet therapy.

Limitations

First, this is an observational study, meaning the generalizability of its findings are limited. Correlations can be used on the population observed, but causality cannot be concluded. Second, there was a relatively small number of patients who were taking CCBs, which again limits the generalizability of such a study, and in particular- the differential effects of dihydropyridine versus non- dihydropyridine and P-gp inhibiting versus non- P-gp inhibiting CCBs. Third, clinical outcomes were not measured in this study, which are necessary to understand what the aforementioned observations related to HAPR entail in terms of adverse cardiovascular clinical outcomes. Specifically, a study assessing the impact of CCBs-induced HAPR on the risk of thrombotic events is warranted. Nevertheless, as mentioned previously, other studies have concluded that an increased rate of HAPR confers a worse prognosis. Fourth, this is a retrospective study, which can lead to hindsight bias.

Conclusions

The current study reports a significant association between an increase in aspirin resistance, measured by both mean ARU and the rates of HAPR, and the use of CCBs. These findings provide a better understanding of the pharmacologic interaction between CCBs and aspirin in patients with stable CAD.

Declarations

Author Contribution- All authors contributed to the study conception and design. Material preparation, and data collection were performed by Afek Kodesh, Liat Sasson, Eli Lev, Alejandro Solodky and Leor Perl. Data analysis was performed by Leor Perl. Figures were made by Leor Perl. The first draft of the manuscript was written by Afek Kodesh and Leor Perl and all authors read and edited the manuscript. All authors read and approved the final manuscript.

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Data Availability - Original research data will be available upon request.

Conflict of Interest/Competing Interests - All authors declare they have no conflicts of interest.

Ethics Approval- All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate- Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1 Baseline Characteristics of patients in the CCB and control groups

Characteristic	CCB Group (n-88)	Controls (n-415)	P-value
Age (years)	67.9 9.7	66.5 11.4	.288
Male sex (%)	77.3	82.9	.214
BMI (kg/m ²)	28.5 3.5	28.0 12.0	.732
CKD (%)	23.5	23.5	.231
Diabetes Mellitus Type 2. (%)	34.7	36.9	.121
Hypertension (%)	83.9	63.5	0.00
Hyperlipidemia (%)	85.1	83.0	.642
Current Smoker (%)	38.0	35.1	.786
Family History (%)	54.8	56.4	.787
Prior MI (%)	47.1	59.7	.031
Prior CABG (%)	34.9	34.5	.933
Prior PCI (%)	52.9	64.0	.039
MVD (%)	52.3	42.4	.091
Statins (%)	89.5	90.7	.747
Beta Blockers (%)	88.4	72.6	.097
ACE Inhibitors (%)	72.6	62.0	.065

CCB = calcium channel blockers; BMI = body mass index; CKD = chronic kidney disease; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; MVD = multi-vessel disease; ACE = angiotensin converting enzymes.

Table 2 Rates of resistance to aspirin of patients in the CCB and control groups

Characteristic	CCB Group (n-88)	Controls (n-415)	P-value
ARU	465.4 70.0	445.2 60.0	.006
HAPR (%)	15.9 36.8	7.0 25.5	.006

CCB = calcium channel blockers; ARU = aspirin reaction units; HAPR = high on-aspirin platelet reactivity.

Table 3 Binary Logistic Regression Analysis for HAPR

Variable	Odds Ratio (OR)	95% CI	p-value
Sex: Male	1.33	0.23 - 8.68	.721
Age	1.02	0.92 - 1.17	.873
Chronic Kidney Disease	1.18	0.28 - 6.32	.861
Diabetes Mellitus Type II	2.21	1.26 - 4.34	.038
BMI	1.04	0.89 - 1.21	.642
Hypertension	0.59	0.13 - 2.21	.423
Current Smoker	0.79	0.28 - 2.11	.131
Hyperlipidemia	0.21	0.32 - 1.84	.152
Prior MI	0.90	0.22 - 4.41	.908
Type of CCB	0.98	0.23-3.74	.427
CCB	1.72	1.04 - 8.91	.047

HAPR= high on-aspirin platelet reactivity; BMI = Body mass index; MI = Myocardial infarction; CCB = Calcium channel blockers.

Figures

Fig. 1

Figure 1

Percentage of patients with HAPR Percentage of patients with high on-aspirin platelet reactivity (HAPR) according to whether patients are taking calcium channel blockers (CCB). Mean rates are shown, with CCB-medicated patients having HAPR response rates of 15.9% and control patients with 7.0%

Fig. 2

Figure 2

Mean ARU of patients Mean aspirin reaction units (ARU), according to whether patients are taking calcium channel blockers (CCB). Mean rates are shown, with CCB-medicated patients having ARU response rates of 465.5 ARU and control patients with 445.2 ARU