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Platelet Inhibition by 81 and 325 mg Aspirin Daily in Men vs. Women without Clinically Apparent Cardiovascular Disease

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Abstract

Compared to men, women have greater platelet aggregation before and after low-dose aspirin. It is not known whether high-dose aspirin therapy brings residual platelet aggregation in women closer to men. Our objective was to compare the inhibition of platelet aggregation in women and men after low and high-dose aspirin. We enrolled healthy subjects (N=106) in a trial of 14 days of aspirin 81 mg/day followed by 14 days of 325 mg/day. Platelet function was measured at baseline and following both aspirin doses. Women had greater baseline platelet activation measures. After both aspirin doses, both sexes had near complete suppression of platelet aggregation to arachidonic acid in whole blood and in platelet-rich plasma (PRP), the direct cyclooxygenase-1 (COX-1) pathway affected by aspirin. For indirect pathways, women had significantly greater residual platelet activation to collagen and adenosine diphosphate (ADP) in whole blood after both aspirin doses and in response to collagen and ADP in PRP after aspirin 325 mg/day only. After aspirin 325 mg/day, women continued to have greater residual platelet aggregation compared to men after aspirin 81 mg/day in response to collagen ($p=0.016$ in whole blood and $p=0.037$ in PRP), ADP ($p<0.001$ in whole blood and $p=0.012$ in PRP), and epinephrine ($p=0.03$ in PRP). Excretion of urinary thromboxane metabolite (urinary 11-dehydro thromboxane B2) decreased after aspirin to a similar extent in both sexes. In conclusion, women continue to have greater residual platelet activity after high-dose aspirin even when compared to men treated with a lower dose of aspirin.

Keywords

Aspirin; Platelet aggregation; Arachidonic acid; Cyclooxygenase-1

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Introduction

Even in the absence of aspirin, women have greater platelet activation compared to men in response to multiple agonists¹. After low-dose aspirin therapy and despite complete and equal suppression of the cyclooxygenase 1 (COX-1) pathway, women continue to have higher platelet aggregation as compared to men, suggesting women may derive lesser cardioprotection from aspirin¹. A sex-specific meta-analysis of 6 large primary prevention trials comparing low-dose aspirin versus placebo found a 14% reduction in cardiovascular events and 32% reduction in myocardial infarction in men but could not find significant protection with aspirin in women². In clinical trials that enrolled women and were included in this meta-analysis, aspirin dose ranged from 50 mg to 100 mg/day. It has been suggested that, in order to reduce the risk of cardiovascular events, women may need larger aspirin doses³. However, the extent to which increased aspirin dose can suppress residual platelet reactivity in women is unknown. Therefore, we compared the effect of aspirin at 81 and 325 mg/day on platelet reactivity in women and men at increased risk of cardiovascular disease.

Methods

The study sample included 106 unaffected apparently healthy family members of 65 patients with documented coronary artery disease events prior to 60 years of age, including brothers and sisters, adult offspring 21 years of age and older, and the co-parent of the adult offspring. Subjects were studied at baseline, after 14 days of 81 mg/day of aspirin, and after 14 days of 325 mg/day of aspirin (Figure 1). Subjects were recruited from the Genetic Study of Aspirin Responsiveness (GeneSTAR), an ongoing study designed to examine genetic determinants of platelet responsiveness to low dose aspirin. The details of the study design and characteristics of the study population have been described earlier¹. Subjects with known coronary artery disease, stroke, any vascular disease, any bleeding or hematologic disorder, a history of hemorrhage, serious medical comorbidity (e.g. renal or hepatic failure, AIDS, cancer, or autoimmune disease), glucocorticosteroid use, or anticoagulant use were excluded. Family members were also excluded if they had a baseline platelet count < 100,000/mL or > 500,000/mL, hematocrit < 30%, or white blood cell count >20,000/mL. Non-study aspirin, other antiplatelet agents, and nonsteroidal anti-inflammatory drugs were proscribed throughout the study period beginning 2 weeks prior to baseline platelet function measurement. This sample size had >90% power to detect an agonist-induced platelet aggregation difference of 4 ohms between men and women. The Johns Hopkins Institutional Review Board approved the study and all participants provided written informed consent.

At baseline, participants underwent a complete cardiovascular history and physical examination and all medications were reviewed by a nurse practitioner. Blood pressure was measured at rest using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Guidelines⁴. Hypertension was defined as a blood pressure $\geq 140/90$ mmHg (average of 4 blood pressure measurements) and/or the use of an antihypertensive medication. Height and weight were measured and body mass index was calculated as weight (kg)/height (m²). Serum glucose and total cholesterol, high density lipoprotein cholesterol (HDL-C), and triglycerides were measured after a 12-hour overnight fast using a Cholestech LDX analyzer (Cholestech Corporation, Hayward, CA). Low density lipoprotein cholesterol (LDL-C) was estimated using the Friedewald formula⁵. Diabetes was defined as having a fasting plasma glucose level ≥ 126 mg/dL and/or taking a hypoglycemic agent. Participants were classified as smokers if they reported smoking any cigarettes within the past month or had an exhaled carbon monoxide measurement of ≥ 8 ppm on 2 successive readings.

Platelet function testing was performed at baseline, after 14 days of therapy with aspirin 81 mg daily, and after 14 days of therapy with aspirin 325 mg daily. Adherence to aspirin therapy was assessed at the end of therapy with each dose of aspirin by a modified Hill-Bone compliance questionnaire⁶ and pill counts. Measurement variation was minimized by having the same technician process the same individuals on the same equipment for the pre- and post-aspirin visits. Platelet technicians were blinded to the sex of participants.

Blood was obtained from venipuncture and collected into vacutainer tubes containing EDTA (for complete blood counts) or 3.2% sodium citrate (for platelet function testing) after discarding the first 4 ml. Platelet counts were determined by automated cell counter (AcT-diff, Beckman-Coulter, Miami, FL). Platelet rich plasma (PRP) was prepared from whole blood by centrifugation at $180 \times g$ for 15 minutes, and platelet poor plasma was prepared by centrifugation at $2000 \times g$ for 10 minutes. Platelet counts were adjusted to 200,000/ μ L by diluting PRP with platelet poor plasma. Plasma fibrinogen was measured on an automated optical clot detection device (Behring Coagulation System, Dade-Behring, Inc, Newark, DE).

Whole blood impedance aggregometry was measured in a Chrono-Log dual-channel lumi-aggregometer (Havertown, PA) after stimulating samples with collagen 5 μ g/ml, adenosine diphosphate (ADP) 10 μ M, or arachidonic acid 0.5 mM. Optical aggregometry in PRP was measured in a 4-channel PAP-4 Aggregometer (Horsham, PA) after stimulating samples with collagen 5 μ g/ml, ADP 10 μ M, arachidonic acid 1.6 mM, or epinephrine 10 μ M. Peak platelet responses within 5 minutes of agonist stimulation were recorded for aggregation (as percent aggregation for PRP and ohms for whole blood). Thromboxane production in vivo was assessed by urinary 11-dehydro thromboxane B₂. Urinary thromboxane was quantified by commercially available enzyme-linked immunosorbent assays (Cayman Chemical Co., Ann Arbor, Michigan) and normalized to urinary creatinine.

Descriptive analyses were performed using means ($\pm$ 1 standard deviation) of continuous variables and frequencies and percentages for categorical variables. Tests for normality of continuous variables were performed using the Wilk-Shapiro tests and variables were log-transformed for significance testing. Simple bivariable relationships were examined using t-tests on the transformed quantitative outcome measures or Wilcoxon tests on the measures that could not be transformed (post-aspirin arachidonic acid), and linear regression models were constructed to predict appropriately transformed platelet function outcomes. Multivariable logistic regression analyses were used to examine dichotomous platelet function outcomes. Regression analyses were performed using the generalized estimating equations to adjust for any intrafamilial correlations. All significance testing was two-tailed with an alpha of 0.05. Data were analyzed using SAS (version 9.1, 2002–2003, SAS Institute, Inc., Cary, NC) and SUDAAN (version 9.0.1, 2005, Research Triangle Institute, Research Triangle Park, NC).

Results

Women enrolled in the study were older, had lower hematocrit, and higher platelet count, serum fibrinogen levels, and HDL-C (Table 1). There were no significant differences between men and women with respect to other cardiovascular risk factors. All patients completed the study, with no drop-outs. Pill counts and self-reported non-adherence showed that almost 94% of the subjects took more than 80% of the prescribed doses of aspirin. There were no differences between men and women in adherence to the therapy. All subjects had taken a dose in the 24-hour period preceding the post-aspirin therapy follow-up.

In unadjusted analyses by sex (Table 2), platelet reactivity in all measures was modestly higher in women; however, these differences were statistically significant only for whole blood aggregation in response to 10 μ M ADP. After therapy with either dose of aspirin, most men and women had near complete suppression of platelet aggregation to arachidonic acid (Table 2). The majority of the subjects had platelet aggregation of either zero percent or very close to zero. Small but similar proportions of men and women retained > 10% aggregation in response to arachidonic acid at both doses of aspirin (10% after aspirin 81 mg/day and 5% after aspirin 325 mg/day). Urinary excretion of thromboxane decreased with both doses of aspirin in both sexes. Women continued to have higher excretion of urinary thromboxane metabolites as compared to men although the difference was not statistically significant.

Platelet aggregation in whole blood was significantly greater in women to both collagen and ADP at the 81 mg/day dose (Table 2). Women retained greater platelet activation to collagen and ADP after therapy with aspirin at 325 mg/day, with no incremental suppression seen in either sex with the higher dose. Similar findings were seen with aggregation to collagen and ADP in PRP, except differences between sexes were only significant after therapy with 325 mg/day.

Platelet aggregation to arachidonic acid, the activation pathway directly related to COX-1, was similar in women given 325 mg/day compared to men given 81 mg ($p = 0.56$ in whole blood and $p = 0.40$ in PRP). Similarly, the percentage of women who achieved nonzero platelet aggregation in response to arachidonic acid after therapy with aspirin 325 mg was similar to the percentage of men who achieved non-zero aggregation after therapy with aspirin 81 mg ($p = 0.48$ in whole blood and $p = 0.73$ in PRP). Although excretion of urinary thromboxane metabolite was modestly higher in women after therapy with 325 mg daily as compared to men after therapy with aspirin 81 mg daily, the difference was not statistically significant ($p = 0.99$).

For pathways that are indirectly related to COX-1, residual platelet aggregation after therapy with aspirin 325 mg was significantly higher in women than in men treated with aspirin 81 mg. After therapy with aspirin 325 mg, women continued to have higher residual platelet aggregation than men in response to collagen ($p = 0.016$ in WB, and $p = 0.037$ in PRP), ADP ($p = <0.001$ in whole blood, and $p = 0.012$ in PRP), and epinephrine ($p = 0.03$ in PRP) as compared to men treated with aspirin 81 mg daily.

In multivariable analyses (Table 3), post-aspirin therapy values were adjusted for pre-aspirin therapy values and for risk factors associated with platelet aggregation including age, race, sex, blood cell counts, smoking, body mass index, blood pressure, and cholesterol, glucose, and fibrinogen levels. In all analyses, the greatest contribution to the total variance in aggregation outcomes was the baseline level of aggregation. In all models, there were no statistically significant differences in aggregation outcomes by sex after adjustment for baseline aggregation level except in response to 10 μ M ADP after aspirin 325 mg. Other factors known to be influential in platelet aggregation contributed little to the total variance, even when statistically significant. In addition to adjusting for differences between the two groups by multivariate linear and logistic regression models (data not shown), we performed two stratified analyses to evaluate the effect of age and race differences between the two sexes. After stratifying by race and mean age, we found the sex-specific direction of aspirin effect on platelet aggregation similar to our main analysis without significant heterogeneity between the subgroups.

Discussion

In this study comparing 2 low doses of aspirin in clinically unaffected individuals from families with premature coronary artery disease, we found baseline differences in platelet function between men and women that became even more prominent after aspirin therapy. Aspirin in either dose showed less suppression in collagen and ADP-induced platelet activation. Women were more reactive in these pathways than men both after 81 mg/day and 325 mg/day of aspirin, with no statistically significant incremental suppression at the higher dose. Even with the higher aspirin dose of 325 mg daily, women retained greater platelet activation in indirect COX-1 pathways compared to men treated with 81 mg/day. In contrast, for platelet activation directly related to COX-1, we found marked suppression of platelet function by aspirin at both 81 mg/day and 325 mg/day in both sexes. Both men and women showed near complete suppression of platelet aggregation to arachidonic acid at 81 mg/day, with no incremental suppression at 325 mg/day. Residual urinary thromboxane excretion after aspirin was not significantly different between sexes, although women again showed slightly greater platelet activation in this measure after both aspirin doses. There was no evidence that any differential distribution of risk factors by sex including age, race, body mass index, blood cell counts or aspirin adherence accounted for the higher residual platelet activation in aspirin-treated women.

Three randomized clinical trials that compared aspirin therapy with placebo in women did not find an advantage of aspirin therapy for primary prevention of cardiovascular diseases. In the Primary Prevention Project trial⁷, the dose of aspirin used was 100 mg, while the Hypertension Optimal Treatment trial⁸ used 75 mg and the Women's Health Study⁹ used the equivalent of 50 mg of aspirin daily. As none of the trials used aspirin at doses greater than 100 mg/day, it has been hypothesized that the lowest effective dose of aspirin to prevent MI in women is greater than 100 mg daily³. Although our study cannot address this hypothesis directly, we found greater platelet reactivity in women than men in indirect COX-1 pathways at both 81 mg/day and 325 mg/day without incremental suppression at the higher dose. Given these findings, it would seem unlikely that a higher dose of aspirin would provide more effective thromboprophylaxis in women.

Our findings that a higher dose of aspirin does not result in a significant incremental suppression of residual platelet activity is in contrast to a recently reported study which found a decrease in aspirin resistance in a secondary prevention population when an aspirin dose of 81 mg/day was also compared with 325 mg/day¹⁰. Several factors may explain this apparent discrepancy including the nature of the study population and platelet outcome definitions. Subjects had known coronary artery disease as compared to healthy subjects without coronary artery disease in our study. Further, importantly, the study simply dichotomized data from platelet function tests into the presence or absence of arbitrarily-defined "aspirin resistance" while we used the full data in continuous form to study the effect of different aspirin doses across the range of platelet function values.

Our study has some possible limitations. The underlying nature of the parent trial of 81 mg/day of aspirin did not allow a wash-out period before beginning the higher dose. This would be particularly important if one saw a difference between the low and high doses, in either sex, which we did not. Both men and women underwent the same treatment regimen and sequence, so that the differential impact of dose by sex observed is unlikely to be the result of the design. In addition, platelets turn over very quickly¹¹ (approximately 10% per day), so that the platelets exposed to the higher aspirin dose did not represent the same pool as those exposed to the lower dose, 14 days prior. Another concern may be the lack of a placebo control group. The inhibitory effect of aspirin on the COX-1 pathway is so potent that any possibility for persons taking a placebo to approximate the biological outcomes

achieved with aspirin would be virtually nonexistent. Furthermore, the pre-post design of our study helps in eliminating most extraneous sources of variation by observing the same individual before and after treatment¹². Finally, it could be argued that our study did not evaluate the impact of platelet function and response to different doses of aspirin on clinical outcomes. This was not possible in a short-term study, but it has been shown that less inhibition of platelet activation both ex vivo¹³ and in vivo¹⁴ is associated with future myocardial infarction and stroke.

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Figure 1.**Study Design**

Four weeks prior to the start of the study, participants were advised not to take aspirin, nonsteroidal antiinflammatory drugs (NSAIDS), or other antiplatelet agents. Demographic and clinical information was obtained and platelet function tests were performed at baseline. Subjects took aspirin 81 mg daily for 14 days and platelet function tests were repeated at the end of day 14. Subjects took aspirin 325 mg daily for an additional 14 days and platelet function tests were again repeated at day 28 of the study.

Table 1

Baseline Sample Characteristics by Gender (N=106)

Variable	Men (N=41)	Women (N=65)	p-value *
Age (years), mean (SD)	36 (11)	41 (12)	0.04
African-American race	39%	58%	0.05
Current smoking	24%	15%	0.25
Hypertension	15%	22%	0.38
Diabetes Mellitus	10%	8%	0.73
Body Mass Index $\geq$ 30	44%	37%	0.47
White blood cell count (10^9 /L), mean (SD)	6.3 (2)	6.6 (2)	0.42
Hematocrit (%), mean (SD)	45 (3)	39 (3)	<0.001
Platelet count (10^9 /L), mean (SD)	240 (51)	287 (69)	<0.001
Total cholesterol (mg/dl), mean (SD)	212 (43)	215 (45)	0.77
Fibrinogen (mg/dl), mean (SD)	340 (99)	405 (111)	0.003

SD = Standard deviation

* Differences by sex were examined using Student's-t tests performed on transformed variables when necessary to achieve normality; categorical variables examined using contingency table arrays and the χ^2 statistic.

Comparison by Sex of Platelet Function Test Results at Baseline, After Therapy with Aspirin 81 mg Daily, After Therapy with Aspirin 325 mg Daily

Table 2

Variable	Baseline		Aspirin 81 mg		Aspirin 325 mg	
	Men	Women	Men	Women	Men	Women
Whole Blood Direct COX-1 Pathway						
Aggregation to arachidonic acid 0.5 mM (ohms)	12.2 (3.9)	13.5 (4.1)	0.7 (2.4)	1.3 (3.6)	1.1 (3.6)	1.1 (4.3)
Platelet Rich Plasma Direct COX-1 pathways						
Aggregation to arachidonic acid 1.6 mM (%)	60.0 (33.4)	58.3 (34.4)	2.9 (2.4)	4.4 (10.1)	5.6 (11.5)	4.1 (10.5)
Whole blood indirect COX-1 Pathway						
Aggregation to Collagen 5µg/ml (ohms)	19.9 (5.9)	22.2 (6.2)	0.05	16.2 (5.8)	19.3 (6.3)	19.2 (6.1)
Aggregation to ADP 10µM (ohms)	9.7 (4.2)	13.0 (3.8)	<0.001	9.3 (4.6)	12.6 (4.4)	13.1 (4.2)
Platelet Rich Plasma Indirect COX-1 pathways						
Aggregation to collagen 5 µg/ml (%)	85.6 (8.7)	83.6 (18.4)	0.49	37.2 (19.8)	43.9 (22.0)	47.9 (21.1)
Aggregation to epinephrine 10 µM (%)	49.8 (35.7)	60.9 (33.8)	0.13	21.4 (11.9)	26.1 (16.0)	27.8 (15.9)
Aggregation to ADP 10µM (%)	68.2 (16.0)	70.2 (19.3)	0.61	61.0 (14.4)	66.2 (13.9)	66.6 (12.1)
Urinary Thromboxane Direct COX-1 pathway						
TxM (ng/mmol creatinine)	236.8 (203)	305.5 (533)	0.69	50.4 (39)	65.3 (69)	58.5 (81)

COX-1 = Cyclooxygenase 1, ADP = adenosine diphosphate, TxM = urinary 11-dehydro thromboxane B2

* Data are presented as nontransformed means (SD); between sex/dose significance testing was performed on appropriately transformed variables using Student's t-tests for continuous variables, and for categorical variables using contingency table arrays and the χ^2 statistic.

Table 3

Multivariable Linear Regression Models Predicting Post-aspirin Platelet Aggregation in Whole Blood After 81 mg and 325 mg of Aspirin

	Aspirin 81 mg				Aspirin 325 mg			
	Model 1: Post-aspirin Aggregation (ohms) to 5 µg/ml Collagen	* r ²	P Value	Beta (SE)	Model 2: Post-aspirin Aggregation (ohms) to 10 µM ADP	* r ²	P value	Model 2: Post-aspirin Aggregation (ohms) to 10 µM ADP
	Beta (SE)				Beta (SE)			Beta (SE)
Age (years)	0.002 (0.04)	0.000	0.97	0.019 (0.034)	0.001	0.58	0.028 (0.048)	-0.002 (0.025)
Female sex	0.975 (1.38)	0.007	0.48	0.206 (0.988)	0.000	0.84	1.772 (1.285)	1.736 (0.864)
White race	-0.206 (1.29)	0.031	0.87	0.122 (0.822)	0.000	0.88	-1.427 (1.184)	-0.676 (0.832)
Current smoker	2.212 (1.36)	0.022	0.11	1.90 (0.853)	0.013	0.03	2.210 (1.369)	0.894 (0.844)
Body mass index ≥ 30	-0.009 (0.071)	0.000	0.90	0.037 (0.050)	0.002	0.47	0.093 (0.079)	0.047 (0.052)
Systolic blood pressure (mmHg)	-0.074 (0.040)	0.034	0.07	-0.046 (0.026)	0.011	0.08	-0.043 (0.037)	-0.038 (0.029)
Glucose (mg/dl)	0.004 (0.008)	0.000	0.60	0.011 (0.011)	0.007	0.30	-0.016 (0.009)	0.001 (0.006)
Total cholesterol (mg/dl)	-0.015 (0.013)	0.01	0.24	0.005 (0.007)	0.002	0.50	-0.002 (0.011)	0.009 (0.008)
White blood cell count (10 ⁹ / L)	0.027 (0.322)	0.000	0.93	-0.188 (0.197)	0.005	0.34	0.126 (0.432)	-0.193 (0.340)
Hematocrit (%)	-0.023 (0.153)	0.000	0.88	-0.084 (0.112)	0.012	0.46	-0.135 (0.158)	-0.022 (0.110)
Platelet count (10 ⁹ / L)	0.001 (0.008)	0.000	0.88	0.008 (0.005)	0.006	0.15	-0.011 (0.009)	0.008 (0.007)
Fibrinogen (mg/dl)	0.01 (0.008)	0.025	0.17	0.005 (0.004)	0.025	0.15	-0.005 (0.008)	-0.002 (0.005)
Baseline aggregation value [†]	0.501 (0.110)	0.3	<0.001	0.621 (0.094)	0.397	<0.001	0.393 (0.101)	0.522 (0.111)
Total Model R ²		0.407				0.482		

ADP = Adenosine diphosphate, SE = standard error

* ² r² is the portion of the total variance in the model explained by each variable; R² is the total variance in each outcome explained by all variables in the model.

[†]The baseline aggregation value represents the agonist and dose specific aggregation for each individual. Thus all post-values in the regression analyses are adjusted for the pre-values.