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Rapid Platelet Inhibition After a Single Capsule of Aggrenox®: Challenging a Conventional Full-Dose Aspirin Antiplatelet Advantage?

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Aggrenox® is a novel combination of 25 mg of aspirin with 200 mg of sustained release dipyridamole. In a recent large trial (ESPS-2), Aggrenox® was twice as effective for secondary stroke prevention as either aspirin or dipyridamole alone, suggesting superior platelet inhibition for combination therapy. We sought to compare the time course of platelet inhibition with Aggrenox® compared with escalating doses of non-enteric coated aspirin. Data from 10 healthy volunteers were analyzed. Fasting subjects sequentially ingested aspirin in the following order: 325 mg, 81 mg, 25 mg, and then one pill of Aggrenox® after a 3-week interval for aspirin washout. Platelet function was assessed at baseline, 15, 30, 60, and 120 min post-medication with 5 μM epinephrine and 5 μM ADP using conventional aggregometry. Aspirin provided significant ($P < 0.01$) reduction of platelet aggregation at 15 min post 325 mg, 30 min post 81 mg, and unexpectedly within 60 min after taking 25 mg of aspirin. A single pill of Aggrenox® also inhibited platelet aggregation within 1 hr after administration. Aspirin inhibits platelets remarkably fast. Both Aggrenox® and a matching dose of aspirin (25 mg) exhibit significant antiplatelet properties within 60 min after ingestion. These findings could be relevant for the optimal balance between the reduction of vascular events via sufficient and rapid platelet inhibition and low risk of bleeding complications associated with the Aggrenox® therapy. Am. J. Hematol. 72:280–281, 2003. © 2003 Wiley-Liss, Inc.

Key words: platelet aggregation; aspirin; dipyridamole; Aggrenox®

Aspirin (ASA) is an established agent for preventing recurrent stroke and acute coronary events. Until recently ASA was the only medication proven to be beneficial for stroke prevention [1], providing risk reduction for ischemic stroke of 39 events per 10,000 treated patients [2]. Aggrenox®, a novel combination of low-dose (25 mg) aspirin with 200 mg of extended-release dipyridamole, is presently approved by the Food and Drug Administration for secondary stroke prevention. The large European Stroke Prevention Study (ESPS-2) revealed that Aggrenox® was twice as effective (37% risk reduction) for secondary stroke prevention as either aspirin (18% risk reduction) or dipyridamole (16% risk reduction) alone [3]. It is not yet clear why combination therapy should yield such a substantial clinical advantage over monotherapies; however, some experimental data suggest that antiplatelet effects could be critical. Indeed, dipyridamole combined with low-dose aspirin in ratios of about 8:1 is much more effective in inhibiting thrombus formation than is a ratio of 1:1 (with more conventional ASA doses) [4]. Recognizing that, in addition to the dose, the onset of platelet inhibition could be essential, we sought to compare how rapidly Aggrenox® and escalating doses of non-enteric coated aspirin will inhibit platelets in volunteers with risk factors for vascular disease.

The study was approved by the Sinai Hospital Institutional Review Board. Subjects were eligible if they met

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TABLE I. Demographic and Risk Factors

Age (years)	41.63 ± 8.76
Male	7 (64%)
Female	4 (36%)
Ethnic origin	
Caucasian	11 (100%)
Smoking history	
Active smoker	6 (55%)
Never smoked	5 (45%)
Vascular risk factors	
Family history of CAD	8 (73%)
Sedentary lifestyle	6 (55%)
Diabetes mellitus	1 (9%)
Hypertension	2 (18%)
Morbid obesity	2 (18%)
Hypercholesterolemia	2 (18%)
Concomitant medications	
ACE inhibitors	1 (9%)
Ca-channel blockers	1 (9%)
Statins	2 (18%)

all of the following inclusion criteria: males and females 21 years and older; conscious and coherent; documented history of vascular disease or three out of the eight well-known risk factors for vascular disease (family history of vascular disease; sedentary lifestyle; diabetes mellitus; hypertension; morbid obesity; known history of hypercholesterolemia; post-menopausal or post-oophorectomy females; current or recent smokers); available and willing to return for follow-up tests; and provision of signed informed consent. Subjects were ineligible for the study if they had participated in another clinical trial within 30 days; had received ASA or any ASA containing medication within the past 3 weeks; had received GP IIb/IIIa inhibitors or thienopyridines within the past 3 weeks; known history of low platelet count; or bleeding disorder. Data from 11 subjects were analyzed. Fasting subjects sequentially ingested ASA in declining concentrations of 325 mg, 81 mg, 25 mg, and then one pill of Aggrenox® after a 3-week interval between doses for ASA washout. Platelets were assessed at baseline and at 15, 30, 60, and 120 min post-medication.

We employed 5 μM epinephrine and 5 μM ADP-induced conventional aggregometry for assessing platelet function. All comparisons were calculated by Mann–Whitney *U*-test to identify specific differences in platelet aggregation.

Demographics and risk factors are presented at Table I.

The baseline blood samples were drawn between 8 and 12 A.M. to avoid diurnal influences. The post-medication samples were collected at 15, 30, 60, and 120-min. To avoid possible observer bias, blood samples were coded and blinded. Individuals unaware of the protocol performed sampling procedures and platelet studies. Combined data of platelet aggregation are presented in Table II.

TABLE II. Onset of Platelet Inhibition Dependent on a Dose of ASA

Time point/ platelet agonist	ASA 325 mg	ASA 81 mg	ASA 25 mg	Aggrenox®
Baseline ADP 5 μM	74.7 ± 2.9	76.0 ± 8.3	76.0 ± 8.6	77.68 ± 8.0
Baseline EPI 5 μM	83.4 ± 4.6	85.8 ± 5.8	85.1 ± 7.9	85.61 ± 7.9
15 min ADP 5 μM	32.0 ± 8.4[a]	63.9 ± 7.7	78.0 ± 6.9	75.9 ± 9.2
15 min EPI 5 μM	10.1 ± 4.2[a]	71.5 ± 8.2	82.2 ± 6.8	81.6 ± 8.0
30 min ADP 5 μM	35.1 ± 4.1[a]	41.9 ± 6.2[a]	70.4 ± 10.1	67.1 ± 9.3
30 min EPI 5 μM	5.1 ± 2.1[a]	8.4 ± 4.7[a]	74.8 ± 7.6	77.0 ± 5.6
60 min ADP 5 μM	37.5 ± 2.3[a]	40.1 ± 5.6[a]	47.9 ± 10.2[a]	44.62 ± 4.4[a]
60 min EPI 5 μM	4.1 ± 3.0[a]	5.2 ± 1.8[a]	15.7 ± 17.0[a]	10.36 ± 7.9[a]
120 min ADP 5 μM	36.0 ± 4.8[a]	36.5 ± 5.4[a]	46.0 ± 9.6[a]	40.30 ± 6.2[a]
120 min EPI 5 μM	3.5 ± 1.2[a]	6.3 ± 2.2[a]	8.4 ± 16.4[a]	8.06 ± 5.0[a]

[a]$P < 0.05$.

Aspirin provides significant reduction of platelet aggregation at 15 min post 325 mg, 30 min post 81 mg, and unexpectedly within 60 min after taking 25 mg of aspirin. A single pill of Aggrenox® also inhibited platelet aggregation within 1 hr after administration.

This study reveals that ASA, even in a very low dose, inhibits platelets remarkably fast. Both Aggrenox® and matching dose of aspirin (25 mg) exhibit significant antiplatelet properties within 60 min after digestion. Indeed, ADP-induced aggregation was decreased by almost 50% and by 90% when platelets were stimulated by epinephrine. These findings may indicate an optimal balance between the reduction of vascular events via sufficient and rapid platelet inhibition and low risk of bleeding complications associated with Aggrenox® therapy. Considering that Aggrenox® reduces the risk of stroke by 23% over ASA alone, the cohort of coronary artery disease population should not be overlooked. Further well-designed and carefully conducted clinical trials should elucidate the potential benefits of Aggrenox® in multiple thrombotic conditions far beyond ischemic stroke, including vascular disease in general and acute coronary syndromes in particular.

REFERENCES

1. Albers GW, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke. Chest 1998;114(5 Suppl):683S–698S.
2. He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. J Am Med Assoc 1998;280:1930–1935.
3. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; 143:1–13.
4. Muller TH, Su CA, Weisenberger H, Brickl R, Nehmiz G, Eisert WG. Dipyridamole alone or combined with low-dose acetylsalicylic acid inhibits platelet aggregation in human whole blood ex vivo. Br J Clin Pharmacol 1990;30:179–186.