Glycoprotein Ibalpha inhibition and ADP receptor antagonists, but not aspirin, reduce platelet thrombus formation in flowing blood exposed to atherosclerotic plaques.

Abstract:
Anti-platelet drugs are used to prevent intra-arterial thrombus formation after rupture of atherosclerotic plaques. Until now, the inhibitory effect of present and future anti-platelet drugs such as aspirin, ADP receptor P2Y(1)/P2Y(12) antagonists and glycoprotein (GP) Ibalpha inhibitors on the interaction of platelets with human plaques is not known. To study those effects we obtained human atherosclerotic plaques by surgical endarterectomy. Plaques induced maximal platelet aggregation in hirudinized platelet-rich plasma (PRP) and blood that was effectively inhibited by aspirin, the P2Y(1) antagonist MRS2179 and the P2Y(12) antagonist AR-C69931MX, but not by GPIbalpha blockade with the mAB 6B4. Inhibition of platelet aggregation by MRS2179 was 74 +/- 37% and 68 +/- 20%, by AR-C69931MX 94 +/- 7% and 80 +/- 6%, and by aspirin 88 +/- 19% and 64 +/- 28%, in PRP and blood, respectively (mean +/- SD; n = 6-12 with plaques from 6 patients). The combination of both ADP receptor antagonists completely inhibited plaque-induced platelet aggregation in hirudinized PRP and blood. Under arterial flow conditions (1,500s(-1)), blockade of platelet GPIbalpha resulted in a strong decrease of plaque-stimulated platelet adhesionaggregate formation of 77 +/- 5% (mean +/- SD; n = 4).
Furthermore, MRS2179, AR-C69931MX and their combination
reduced plaque-dependent platelet aggregate formation by 35 +/- 14%, 32 +/- 13% and 58 +/- 12% (mean +/- SD; n = 5), respectively. Aspirin was without significant effect. In conclusion, a GPIbalpha-blocking antibody, as well as P2Y(1) and P2Y(12) receptor antagonists, alone or in combination, reduce in contrast to aspirin human plaque-induced platelet thrombus formation under arterial flow. Although these new anti-platelet agents inhibit platelet thrombus formation after plaque rupture, more efficient platelet blockers are required.