871 Platelet-Active Agents and Their Evaluation

Wednesday, April 1, 1998, 8:30 a.m.–10:00 a.m.
Georgia World Congress Center, Room 257W

8:30

871-1 Unexpected, Discordant Effects of Aspirin on Platelet Reactivity

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Background: Characterization of platelet function in response to antiplatelet agents has been elusive. To determine whether effects of aspirin are consistent, we quantified both platelet activation in whole blood with flow cytometry to detect P-selectin expression and platelet aggregation (by aggregometry in platelet-rich plasma) in healthy subjects before and after 5 days of treatment with aspirin (ASA, 81 and 325 mg qd) or Ticlid (250 mg bid).

Methods and Results: Basal samples were drawn after a 10 day drug free interval. Both platelet activation and aggregation were induced with low rather than conventional supraphysiologic concentrations of ADP (~ 2 μM). Anticoagulation was with corn trypsin inhibitor used to inhibit only Factor XIIa and hence the contact pathway. Responses to ASA were discordant. 45% of subjects were non-responders, 33% were responders, and 22% were paradoxical responders. Respondera showed both decreased platelet activation and aggregation with ASA (% control with 325 mg ASA; activation = 52 ± 7%, aggregation = 73 ± 3%, p < 0.001 for both). Paradoxical responders showed decreased activation with 81 mg ASA (42 ± 11%, p ≤ 0.01) but increased activation with 325 mg ASA (248 ± 46, p < 0.05), both paralleled by corresponding changes in aggregation. In all subjects, Ticlid decreased both activation and aggregation.

Conclusion: Thus, responses to antiplatelet therapy differ markedly among individuals with directionally opposite effects occurring in some with different doses of the same agent.

8:45

871-2 Differential Dose Effect of Aspirin in the Primary Prevention of Myocardial Infarction

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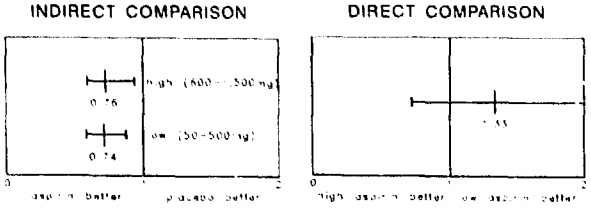
By interfering with platelet aggregation aspirin is effective in the secondary and primary prevention of acute myocardial infarction. Since coronary plaque rupture may be mediated by immunocompetent cells like monocytes, the antiinflammatory effect of high dose aspirin may also contribute to the protection against myocardial infarction, but this has never been evaluated in humans.

To test this hypothesis in the primary prevention of myocardial infarction all 28 suitable randomized controlled trials with noncoronary patients and healthy individuals from the Antiplatelet Trialists' Collaboration were analyzed on aspirin dose in relation to the efficacy in the prevention of myocardial infarction. Both indirect comparisons with placebo and direct comparison between aspirin dose regimens were made.

High dose (600 to 1,500 mg daily) aspirin was compared to placebo in 10,680 patients in 21 trials and found to reduce the incidence of myocardial infarction (RR 0.76, 95% CI 0.60–0.96). Low dose (500 mg or less) aspirin was compared to placebo in 29,201 individuals in 5 trials and found to reduce the incidence of myocardial infarction (RR 0.74, 95% CI 0.63–0.88). In 1,753 patients in 2 trials high dose regimens were directly compared to low dose aspirin and not found to be more effective (RR 1.33, 95% CI 0.84–2.54, see figure).



Thus, in both direct dose comparisons and indirect placebo comparisons high dose aspirin does not prevent myocardial infarction more effectively than low dose aspirin. The antiphlogistic action of high dose aspirin does not seem to contribute to the prevention of myocardial infarction, the inflammatory origin of which is still under debate.

9:00

871-3 Combination of Beraprost Sodium, an Orally Available Prostacyclin Analogue, With Aspirin: A New Promising Anti-Platelet Prescription Against Stroke and Atherosclerosis?

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Background: Aspirin inhibits thromboxane A_2 (TXA_2)-dependent (D) platelet aggregation (AG), however, it can inhibit prostacyclin (PGI_2) synthase and thus may promote platelet AG and atherosclerosis. We aimed to investigate whether a PGI_2 analogue, beraprost sodium (BPS), given to humans in combination with aspirin exerts beneficial effects on platelet functions without causing serious adverse reactions.

Methods: Aspirin (81 mg, per os) and BPS (40 μg, per os) were given alone or in combination to male volunteers (n = 8). We checked 1) platelet AG induced by ADP, collagen (COL) and thrombin (THR), 2) platelet cytosolic Ca^{2+} ($[Ca^{2+}]i$) mobilization induced by THR and COL and 3) plasma concentrations of TXB_2 and 6-keto-$PGF1\alpha$.

Results: Single administration of BPS inhibited both TXA_2-D and TXA_2-independent (ID) AG by 20% and 21%, respectively. Aspirin preferentially inhibited TXA_2-D AG (−60%) compared with TXA_2-ID AG (−12%). Combination of aspirin and BPS exerted an additive effect on inhibition of platelet AG (TXA_2-D AG: −84%, TXA_2-ID AG: −35%). Increases in $[Ca^{2+}]i$ induced by THR, and COL were inhibited by aspirin and/or BPS in a manner parallel to their inhibitory effects on platelet AG. Aspirin and/or BPS did not modify plasma 6 keto-$PGF1\alpha$ levels, and aspirin significantly reduced plasma TXB2 levels by 51%. Combination of aspirin and BPS did not cause any major adverse reactions such as bleeding.

Conclusion: Oral administration of BPS in combination with aspirin exerted potent anti-platelet effects additive to those elicited by aspirin alone. This combination would be clinically useful to prevent thrombosis and progression of atherosclerosis because 1) it enhances anti-aggregating effects of aspirin which is relatively weak, 2) it may compensate for the aspirin-induced reduction of endogenous PGI_2 and 3) it is safe without causing excessive synergistic reactions.

9:15

871-4 Safety of 10 Days of Ticlopidine After Coronary Stenting – A Randomized Comparison With 30 Days: Strategic ALternatives With Ticlopidine in Stenting Study (SALTS)

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Purpose. Thirty days of Ticlopidine (TIC) can result in fatal neutropenia (NEUT). Subacute stent thrombosis (SST) tends to occur within 10 days of stenting. We postulated that 10 days of TIC may be sufficient to prevent SST, yet reduce the likelihood of developing NEUT.

Methods: Pts were randomized to aspirin (325 mg q.d.) and 10 or 30 days of TIC (250 mg b.i.d.) post elective Palmaz-Schatz stent (≤2) placement. Post-stent high-pressure balloon inflations were used (no IVUS used in any pts). Exclusion criteria include LVEF < 30%, AMI within 2 days of stenting and ostial lesions. Complete blood counts were requested at 2, 4 and 6 weeks after discharge in all pts.

Results: To date, 30-day follow-up results of 99 pts.

	10 days TIC (N = 58)	30 days TIC (N = 41)	P Value
Age (yrs)/Males (%)	61/67	63/88	NS/NS
Stable/Unstable Angina	36%/47%	24%/56%	NS/NS
Recent MI (%)	17	15	NS
LVEF (%)	48	49	NS
Stent in CABG (% of pts)	17	7	NS
Stent diameter (mm)	3.3	3.4	NS
Number of stents/case	1.3	1.3	NS
Major adverse events*	1	3	0.03

* 10 day TIC - thrombocytopenia, 30 day TIC - SST, NEUT, death

Conclusion: Ten days of TIC post Palmaz Schatz stenting is safe and effective. Further data will determine if NEUT or TCP is reduced using only 10 days of TIC. Completed study results will be available by 3/98.