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# **STUDIES OF PLATELET FUNCTION, AND EFFECTS OF ASPIRIN AND CLOPIDOGREL TREATMENT**

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Thoraxklinikens föreläsningssal (N2:U1) Karolinska Universitetssjukhuset, Solna

**Fredagen den 23 september 2011, kl 09.00**

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**Stockholm 2011**

## ABSTRACT

Antiplatelet therapy with aspirin and clopidogrel is a cornerstone in cardiovascular prevention and lowers cardiovascular mortality and morbidity in patient with coronary artery disease (CAD). Mental stress and physical exertion can trigger acute coronary events and prothrombotic responses to stress may contribute to such triggering. Platelet activation seems to contribute to the pathogenesis of preeclampsia.

The dose- and time-dependence of antiplatelets effects of aspirin (37.5 mg/day, 320 mg/day and a single dose of 960 mg) were studied in 15 male healthy volunteers. The variable most sensitive to inhibition by aspirin was arachidonic acid (AA)-induced platelet aggregation in platelet rich plasma, followed by serum TxB<sub>2</sub>. The urinary excretion of 11-dehydro-TxB<sub>2</sub> was less markedly, but dose-dependently reduced by aspirin. The effectiveness of aspirin is thus highly dependent on the assay method used. There was limited inhibition by aspirin of collagen and AA-induced platelet aggregation in hirudinized whole blood and there was recovery of platelet function in whole blood within a normal 24 h dosing interval in healthy volunteers.

The effects of clopidogrel treatment on exercise-induced platelet activation were examined in 15 healthy volunteers who performed an exhaustive exercise test, and in 31 aspirin treated patients with stable CAD who performed a symptom limited exercise test in a randomized, double-blind, placebo controlled study. Strenuous exercise evoked multicellular activation *in vivo* and promoted a prothrombotic state. Clopidogrel treatment inhibited platelet and platelet-leukocyte aggregation evoked by ADP and thrombin (which releases ADP from platelets) stimulation *in vitro* but the acute prothrombotic response to exercise was little influenced by clopidogrel treatment in both aspirin treated CAD patients and healthy volunteers. This indicates that the P2Y<sub>12</sub> receptor is not likely to be of major importance for “stress-induced” platelet activation.

The urinary excretion of 11-dehydro-TxB<sub>2</sub> (TxM) reflects platelet activity *in vivo*. The present work improved the methodology for immunological measurements of TxM in urine, and also showed that such measurements may be performed in plasma for the evaluation of platelet activity. This method showed excellent agreement with the gold standard method based on gas chromatography-mass spectrometry.

Urinary TxM increased throughout normal pregnancy with the highest excretion 3-7 days postpartum. In 28 patients at high risk of suffering preeclampsia urinary TxM was elevated compared to the healthy pregnant women already before gestational week 13. Low-dose aspirin treatment (75 mg once daily) effectively inhibited platelet-dependent thromboxane production early in pregnancy in high risk patients, but urinary TxM increased later during pregnancy. The results support a role for thromboxane in preeclampsia, and suggest that aspirin treatment should be initiated earlier than has been the case in studies which show only modest protective effects of low-dose aspirin.

This thesis shows that both aspirin and clopidogrel have limitations as antithrombotic agents. Some patients at risk may not benefit from adequate aspirin protection against cardiovascular events. One explanation for this result may be our finding of a recovery of platelet function 24 hours after dosing and that pronounced AA-induced platelet aggregation persists in whole blood despite aspirin treatment. “Stress-induced” platelet activation is little influenced by treatment with aspirin and clopidogrel. This information about treatment with aspirin and clopidogrel might be useful in shaping more efficient antithrombotic therapy for patients at high cardiovascular risk.