Effects of a New Antibody Glycoprotein IIb/IIIa inhibitor(IND) on platelet Function, Fibrinogen Binding and Bleeding Time; Results of two Phase I clinical Trials

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The present study describes the first administration of the IND, the Fab fragment of a humanized monoclonal antibody against the fibrinogen GPIIb/IIIa-receptor, in healthy male humans.

Platelet aggregation(induced by 20 μM ADP), platelet adhesion, fibrinogen binding, bleeding time and the IND concentrations in plasma were studied in substudy I after single bolus of 0.025, 0.05, 0.1, 0.2 and 0.4 mg/kg the IND (N=6 for each group) and in substudy II after a bolus(0.35 mg/kg) plus 6 hours infusion at different dose levels of the IND (0.5, 0.75, 1.0, 1.5 μg/(kg · min), N=5-6 per group), with c7E3Fab as reference drug. Bolus injections produced a dose dependent inhibition of platelet aggregation and fibrinogen binding as well as a reduction of platelet adhesion. After the 0.2 mg/kg and 0.4mg/kg bolus, fibrinogen binding was reduced by > 80%, coinciding with a prolongation of bleeding time to approx, 60mins. Bolus followed by infusion of 1.0 and 1.5 μg/(kg · min) the IND maintained inhibition of platelet aggregation> 80% induced by the initial bolus. Aggregation returned to normal within 24 hours and adhesion within 48 hours. Bleeding times returned to normal 4 hours after cessation of the infusion. An i.v. bolus of 0.25 μg/kg of c7E3Fab followed by an infusion of 0.125 μg/(kg · min) showed similar effects to those observed with the 0.5 and 0.75 μg/(kg · min) infusion of the IND.

This IND has shown to effectively inhibited IIb/IIIa mediated platelet aggregation and adhesion in humans. The results of this phase I-study will give rise to further clinical evaluation of the IND.