Kinetics of 24-hour recovery of platelet TXA_2 production: a methodological approach to describe and understand interindividual variability in low-dose aspirin response

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Background. Low-dose aspirin pharmacodynamics relies on the irreversible, cumulative, mainly pre-systemic, inhibition of platelet cyclooxygenase (COX)-dependent thromboxane (TX)A_2 production. COX inhibition in the megakaryocytes and pro-platelets depends on the systemic bioavailability of aspirin. Serum TXB_2 measurement is an *ex vivo* assay reflecting the maximal COX activity in platelets, it relies on the generation of thrombin during blood clotting, which releases arachidonic acid from membrane phospholipids, maximally fuelling COX activity and TXB_2 production. The European Medicines Agency identified serum TXB_2 as the only validated surrogate biomarker of aspirin efficacy. Due to the difference between aspirin half-life (min) and the traditional dosing interval (24hrs), it is crucial to assess if aspirin can steadily inhibit platelet COX-1 over the 24-h dosing interval.

Aims. To investigate the kinetics of TXB_2 inhibition over the 24-hr aspirin dosing interval in different diseases.

Methods. We studied the kinetics of serum TXB_2 recovery by blood sampling every 3 hrs, between 12 and 24hrs after aspirin 100mg in 100 type-2 diabetics and 70 non-diabetics at high cardiovascular risk, all on chronic antiplatelet prophylaxis. TXB_2 values were fitted with a simple linear model ($y=a+bx$), allowing calculation of recovery slopes (ng/ml/hr). Serum TXB_2 was also measured at 12 (n=22) and 24hrs (n=69) after aspirin 100mg in essential thrombocythemia (ET) patients, having a high platelet turnover.

Results. Serum TXB_2 recovery between 12 and 24hrs after dosing was linear and highly variable. Values at 24hrs were significantly higher than 12hrs in each group: diabetics 12hrs: 0.54[0.3-1.1], 24hrs 1.4[0.8-2.3]ng/ml; non-diabetics 12hrs 1.03[0.7-1.53], 24hrs 1.8[1.5-3.2]ng/ml; ET: 12hrs 2.1[1.3-6], 24hrs: 11.43[6-24]ng/ml (all $p<0.01$). The difference in serum TXB_2 between 12 and 24hrs predicted ~90% of the recovery slope variability. In both diabetic and ET patients, TXB_2 recovery slopes were independently predicted by reticulated platelets (directly) and age (inversely). Body Mass Index was a direct predictor only in diabetics. Body weight was an independent predictor in non-diabetics.

Conclusions. Measuring the kinetics of serum TXB_2 recovery over the aspirin dosing interval, especially between 12 and 24 hrs, is useful to unravel variability in platelet response, allowing to design personalized dosing regimens.