

# Pharmacodynamic interaction modeling and personalized drug dosing for antiplatelet therapy

Antonello L. G. Caruso, Gorazd Svetičič, Gisela Scharbert, Sybille A. Kozek-Langenecker, Michele Curatolo and Manfred Morari

## INTRODUCTION

**P**LATELET activation and aggregation play a pivotal role in cardiovascular disease, triggering adverse events such as acute coronary syndrome and stroke. Inhibition of platelet aggregation is therefore a primary therapeutic goal [1].

The present “one-size-fits-all” antiplatelet strategy is flawed [2]. At one end of the spectrum, selected patients with excessively low platelet reactivity may bleed. Patients with high platelet reactivity may on the other hand be subject to ischemic events. Optimal antiplatelet therapy should entail personalizing drug dosage based on an objective assessment of the individual thrombotic potential through measurement of platelet function.

ADP, a potent platelet aggregator, interacts with platelet receptors P2Y1 and P2Y12. MeSAMP prevents ADP-induced activation through P2Y12 inhibition [3-4]. Prostacyclin-mimetic Iloprost inhibits aggregation by stimulating adenylyl cyclase [5]. Quantitation of MeSAMP and iloprost antiplatelet effects has not yet been undertaken.

This study has multiple objectives: i) to investigate the concentration-effect relationship of these drugs; ii) to determine the nature (additivity, synergism, or antagonism) of MeSAMP-iloprost pharmacodynamic (PD) interaction; iii) to find the optimal combination in the individual by taking into account both desired and adverse drug effects (platelet response to ADP and TRAP, respectively).

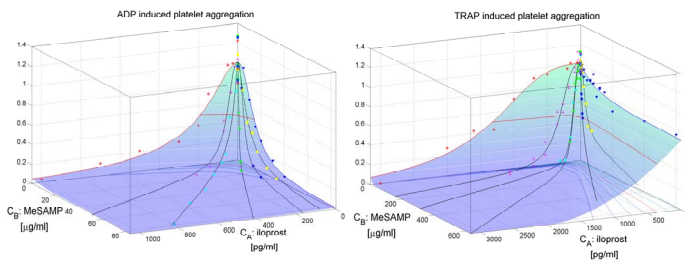


Fig. 1. Interaction response surfaces for drug effects on ADP- (left) and TRAP-induced platelet aggregation (right) for one representative subject. Zoom in for viewing details of model fit (surface and colored lines) to experimental blood coagulation data (symbols).

Manuscript received February 10, 2010.

A. Caruso and M. Morari are with the Automatic Control Laboratory, ETH Zurich, Switzerland (caruso | morari@control.ee.ethz.ch).

G. Svetičič, G. Scharbert and S. Kozek-Langenecker are with the Department of Anesthesiology and Intensive Care Medicine, Vienna Medical University, Austria.

M. Curatolo is with the Department of Anesthesiology, Bern University Hospital, Switzerland.

PHARMACODYNAMIC MODEL PARAMETERS OF DRUG ANTICOAGULANT EFFECTS

Parameter	Mean	SD
C50_iloprost_ADp [pg/ml]	201	104
C50_mesamp_ADp [µg/ml]	8.9	6.1
beta_ADp	-2.0	4.5
C50_iloprost_TRAP [pg/ml]	1122	465
C50_mesamp_TRAP [µg/ml]	71.6	41.4
beta_TRAP	-0.7	3.6

Table 1. Estimated values of single-drug C50s for drug inhibitory effects on ADP- and TRAP-induced platelet aggregation and corresponding interaction parameters in the investigated population (15 healthy adult volunteers, 7 male/8 female).

## MATERIALS AND METHODS

After obtaining written informed consent, blood from 15 healthy adult volunteers was investigated at the Vienna Medical University with Multiplate (Dynabyte, Germany), a novel point-of-care impedance platelet aggregometry device.

## RESULTS

The response surface methodology is used to characterize the whole dose-response relationship of MeSAMP-iloprost regimens. Antiplatelet data are fitted with the Well-being PD model [6] through maximum likelihood estimation procedures (Fig. 1). The identification of PD parameters (most notably, the C50s and PD interaction parameters beta\_ADp and beta\_TRAP for platelet aggregation in response to ADP and TRAP, respectively) was carried out for each individual as well as the population (Table 1). The individual dose optimization results are in agreement with dosages suggested in the literature [7].

The work yields clinically relevant information in terms of PD parameters for antiplatelet drugs administered alone or in combination. Combined with the use of point-of-care devices for the measurement of platelet reactivity, the proposed methodology delivers clinically viable recommendations for optimal personalized drug dosing.

## REFERENCES

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