PK/PD determinants of the interindividual variability in the antiplatelet response: acetylsalicylic acid "resistance" revisited

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Acetylsalicylic acid exerts its antithrombotic activity through a permanent acetylation of a Serine 529 residue of the cyclooxygenase (COX)-1 isoenzyme, causing an irreversible inhibition of thromboxane (TX)A_2 generation from activated platelets. Acetylsalicylic acid pharmacokinetics involves esterases and phase II enzymes, without contribution of the cytochrome P450 system. Inter- and intra-individual variability in the degree of platelet COX-1 inhibition largely depends on acetylsalicylic acid pharmacodynamics.

The renewal rate of COX-1 in platelets and its precursors, the competition at a COX-1 docking site common to acetylsalicylic acid and traditional non-steroidal anti-inflammatory drugs may explain most of the variability in responsiveness, and can be corrected. A pharmacokinetic-based variability can occur in obese subjects and it is predicted by *in silico* models, although further mechanistic studies are needed in severely-obese subjects.

In conclusion, as for most of the drugs, variable response is hooked on acetylsalicylic acid pharmacological characteristics, and understanding the determinants influencing drug response is crucial for personalizing therapy.