Mechanism-based pharmacodynamic modeling for predicting exposure response

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Objectives: A major challenge in drug discovery and development is the prediction, in a strictly quantitative manner, of drug effects in man on the basis of information from in vitro bioassays and/or in vivo animal studies [1]. This impels developing tools with much improved properties for extrapolation and prediction, such as mechanism-based PK-PD modelling and simulation.

Methods: Mechanism-based PK-PD models are based on principles from systems biology and contain specific expressions to characterize processes on the causal path between plasma concentration and response. This includes a) the target distribution, b) the target interaction/activation and c) transduction and the homeostatic control mechanisms, which may be operative. The utilisation of these models relies on novel biomarkers characterising specific processes on the causal path in a quantitative manner. An essential feature of mechanism-based PK-PD models is the strict distinction between “drug-specific” and “biological system-specific” pharmacodynamic parameters to describe in vivo drug effects [2,3,4,5].

The latest development in mechanism-based PK-PD modeling has been the introduction of the concept of disease systems analysis, to characterize drug effects in disease processes and disease progression. Disease systems analysis aims at the distinction between drug effects on the “disease status” versus the “disease process” enabling the prediction of long-term treatment effect [6].

Results: We have successfully developed mechanism-based PK-PD models for drugs acting at various targets including A1 Adenosine, µ Opioid, 5-HT1A Serotonin and GABAergic receptors. Our findings show that in general a drug's in vivo intrinsic efficacy can be accurately predicted on the basis of in vitro bioassays. Prediction of the in vivo potency on the other hand appears to be more difficult, presumably as result of complexities at the level of the target site distribution. Our results also show that equilibrium concentration-effect relationships can be readily scaled from pre-clinical animal models to humans. The utility of this approach has recently been demonstrated for (semi-)synthetic opioids where a mechanism-based PK-PD model has been developed which can predict the clinical analgesic and respiratory depressant effects on the basis of preclinical in vitro and in vivo data [7]. In contrast, the scaling of transduction and homeostatic feedback mechanisms appears to be more complex. An example of the latter is our work on the allometric scaling of different biomarkers for 5-HT1A receptor agonists from preclinical in vitro and in vivo models to man [8]. The first application of disease systems analysis has been in the field of type 2 diabetes mellitus, where it has been shown that drug effects on the deterioration of beta cell function and insulin sensitivity can be quantified by analyzing a cascade of biomarker responses [9].

Conclusions: It is concluded that mechanism-based PK-PD models provide a scientific basis for the prediction of efficacy and safety of novel drugs in humans on the basis information from in vitro bioassays and/or in vivo animal studies.

References:


