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Commentary

PK/PD Modelling and Beyond: Impact on Drug Development

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Abstract. PK/PD modelling will play an increasingly important role in drug development, because it will identify key properties of a drug *in vivo*, allowing the characterization and prediction of the time course of drug effects under physiological and pathological conditions (intensity and duration). It has developed from a descriptive to a mechanism-based approach, taking the relevant processes on the causal path between drug administration and drug effect into account. Recent developments and insights from systems biology and systems pharmacology will provide new information on the complexities of disease associated with the identification of multiple targets for drug treatment. This will give rise to new opportunities of drug combinations, which can only be developed rationally through the appropriate application of dynamical systems-based PK/PD models.

KEY WORDS: mechanism-based PK/PD models; new drug combinations; PK/PD modeling in drug development; systems pharmacology and therapeutics.

BACKGROUND

In the past 25 years much progress has been made in the field of integrated pharmacokinetic–pharmacodynamic (PK/PD) modelling and its application, as can be deduced from the considerable increase in the number of papers in this area published in pharmaceutical and clinical pharmacological journals. This holds both for the modelling aspects per se as well as for its applications in drug development and research on medicines in general. This progress in PK/PD becomes actually also very clear from the Proceedings and Abstracts of the Symposia that LACDR at Leiden/University has organized every 4 years since 1990 under the theme "*Measurement and Kinetics of in vivo Drug Effects. Advances in simultaneous PK/PD modelling*" (1). Dr. Meindert Danhof has always been the principal organizer, each time assisted by key contributors to the field like Drs. Gerhard Levy, Lewis Sheiner, Carl Peck, Jean-Louis Steimer, Don Stanski, Mats Karlsson, Jaap Mandema, Piet-Hein van der Graaf, Bob Powell, Nick Holford and Paul Rolan. The interest for these symposia has considerably increased over the years with contributions from academia as well as from industry, illustrating the recognition of the relevance of PK/PD modelling in drug development. In 1997 we summarized this in a paper with the typical Dutch subtitle "The wooden shoe paradigm" (2). It emphasized that PK/PD should be the steering mechanism throughout the drug development process in order to obtain the information relevant to be put into the drug label. Furthermore it stated that collaboration between the industry, academia and regulatory agencies should be necessary to achieve this. This call for more cooperation was repeated in the FDA Report in 2004 on: "*Innovation or Stagnation. Challenge and Opportunity on the CriticalPath to New Medical Products*" (3). The critical path has to become more innovative and more informative in order to assure that novel medicines will be more effective and safer than existing ones and by necessity take the important issue of "personalized medicine" into account. Integrated PK/PD modelling is a most relevant tool to achieve this and should be considered and implemented at the earliest phases of drug development (4). Also in drug delivery research PK/PD is to become an important aspect in order to assure that advanced drug delivery systems represent added therapeutic value (5).

CURRENT PK/PD MODELLING APPROACHES

The primary objective of PK/PD modelling is to identify key properties of a drug *in vivo*, which allows the characterization and prediction of the time course of drug effects under physiological and pathological conditions (intensity and duration). In the early pioneering studies (e.g. (6)), this was attempted by a rather empirical approach where the model comprised three components: a pharmacokinetic model, characterizing the time course of drug and metabolite concentrations in plasma; a pharmacodynamic model, characterizing the relationship between concentration and effect(s); a link model, which serves to account for the often observed delay of the effect relative to the plasma concentration (e.g. "effect compartment" model). Such models can successfully be applied when the delay in effect is caused by drug distribution to extracellular targets by passive diffusion. However, target distribution kinetics may often be more complex, e.g. for drugs acting on intracellular targets or with a site of action in organs which are protected by specific barriers, e.g. the brain. This

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requires that the role of specific transporters, which either increase or decrease the target-site concentration of the drug, is taken into account. Physiologically-based PK modelling concepts will be helpful to characterize and predict target-site distribution kinetics in such situations.

In recent years a far more mechanism-based approach is being pursued, which features specific expressions to characterize processes on the causal path between drug administration and effect. These include: target site distribution (as discussed), target binding and activation, pharmacodynamic interactions (also with endogenous substances), transduction, homeostatic feedback mechanisms and the effects of the drug on disease progression. A most comprehensive review of this mechanism-based PK/PD modelling has recently been published by Danhof *et al.* (7), which also includes several examples in which such an approach has successfully been applied. A key feature of this mechanism-based approach is the explicit distinction between *drug-specific properties* and *biological system-specific properties*. Drug-specific are those that describe the interaction between the drug and the biological system in terms of target affinity and target activation, whereas system-specific parameters describe the functioning of the biological system per se. The distinction between these two types of parameters appears to be crucial for the prediction of drug effects in humans from *in vitro* and animal experiments. Drug-specific properties like the *in vivo* target affinity and intrinsic efficacy can often be predicted on the basis of *in vitro* bioassays. The values for these properties or parameters often appear to be identical between species, implying that these may not require scaling when applied in inter-species extrapolation. Moreover, there is no or lesser need to take intra- and inter-individual variability in the values of these parameters into consideration. These observations on drug-specific properties have been made for small molecule drugs; it still is to be investigated if these hold for biologicals (proteins, antibodies) as well. On the other hand, biological system-specific parameters (e.g. the level of expression of the target protein or the rate constants of processes at the level of transduction) can only be estimated by *in vivo* systems analysis and usually their values will vary between species, individuals, disease states and other conditions. This implies that interspecies scaling of biological system-specific parameters is required and that intra- and inter-individual variability in these parameters must be taken into account.

Preclinical investigations in suitable experimental animal models (e.g. chronically instrumented ones) are most important to explore and develop a suitable mechanism-based PK/PD model. These often rely on the use of *biomarkers* characterizing the processes on the causal path of drug effects to the ultimate clinical effect. The important concept of *pharmacological transduction* refers to the processes that govern the transduction of target activation into drug response *in vivo*. When such processes are slow *in vivo* (operating at rate constants in the order of hours or even days) they will determine the time course of drug effects. Modelling of such processes is often complex because they are typically non-linear. Furthermore complex homeostatic feedback mechanisms may attenuate or alter drug response in terms of fluctuating effects with time, dependence of drug effects on the rate of administration, tolerance development upon continuous or chronic administration, or the occurrence of rebound phenomena upon cessation of treatment. The latter also is a very important issue to consider in relationship to the often observed patient's poor adherence to the prescribed dosage regimen. Such time-dependent pharmacological transduction mechanisms require PK/PD modelling concepts which are based on dynamical systems analysis. This approach is also applied to the latest important and promising development in PK/PD, i.e. the modelling of disease progression during drug treatment (7,8).

SYSTEMS BIOLOGY AND SYSTEMS THERAPEUTICS

The term dynamical systems analysis links PK/PD modelling with a most important fundamental current development in research in biology at large, i.e. that of "systems biology". During the past 25 years enormous progress has been made in unravelling the (human) genome and high-throughput and bio-informatics technologies have generated an explosion of data at the level of the genome, the proteome and the metabolome. However, this reductionistic approach of generating important data on individual components of a biological system is insufficient to understand the functioning of "life" at the cellular or organ level, let alone that at the level of an entire living organism. Life functions through the continuous and integrated dynamic interactions between the numerous components of a systems network. Systems biology is the branch of biology that aims at studying the functioning of these networks and thereby provide an integrated understanding of how life functions. In several countries all over the world specific institutes have been established in recent years to address this formidable multidisciplinary research challenge, combining expertise from a large number of different disciplines, including mathematics, physics, (bio)chemistry, informatics, technical sciences and biology in all its aspects. An essential central component of such research is the modelling cycle: the iterative cycle of simulations, predictions, experimental verification and new hypothesis generation (9). Through such approaches ultimately key components, or interactions between components, in a network of life may be identified, which constitute normal physiology but also may explain the development of pathophysiology. Once robust models have been established, interventions like pharmacological ones, can be tested in terms of attempting to attenuate specific components of the network which may be associated with efficacy or safety of drug therapy. Of course these are enormously complex approaches, but we will begin to learn more about the multifactorial character of most diseases and thereby realize that our current therapeutic practice of attempting to cure a disease or alleviate its symptoms by one drug that more or less specifically acts at one target in the biological system, is very primitive and inadequate. Through systems biology and systems pharmacology we are likely to identify a number of different key targets in a disease, each of which may require specific pharmacological intervention in order to achieve optimal efficacious and safe treatment. We know already at this moment that different targets may have to be addressed in order to achieve a better treatment and therefore the practice of combination therapies is actually not uncommon in medical practice (e.g. in asthma and hypertension). In the future rational drug combinations will be designed on the basis of

new insights in disease mechanisms including the specific components of the biological systems underlying these. And in order to do that rationally, PK/PD modelling will be an essential tool to evaluate such combinations in assessing their desirable "additive" or "synergistic" effects. Already at this stage PK/PD modelling has proved to be very useful in studying drug–drug interactions (DDIs) *in vivo* (7,10). Currently DDIs are usually considered as undesirable and cumbersome, because they are associated with increased risks during combined treatment. And fixed drug combinations are rather the exception than the rule in current therapeutic practice. However, this may well change in the future on the basis of new insights in disease mechanisms, which require rationally designed and developed fixed drug combinations. This perspective represents exciting new opportunities for drug discovery and development, which will include new chemical entities and biologics, as well as existing molecules which have already been used as medicines for a long time. "Systems therapeutics" will be the result of this, with PK/PD modelling as the most important scientific *in vivo* tool to assess its rationality. Of course this also implies major challenges in clinical drug evaluation, i.e. efficacy and safety assessment (trial designs, statistical analysis, identification of adverse effects etc).

CONCLUSIONS

PK/PD modelling has developed from a descriptive to a mechanism-based approach. In recent years novel concepts of mechanism-based PK/PD modelling have been developed and successfully applied and they potentially constitute a basis for predicting drug effects in humans on the basis of pertinent information from pre-clinical *in vitro* and *in vivo* experimental data. It may be expected that when more detailed information on the biological system becomes available (i.e. on drug transporter function, pharmacological receptor function and regulation, homeostatic feedback mechanisms, disease progression), the accuracy of the predictions will further improve. PK/PD modelling thereby will be a very important tool in efficacy and safety assessment during the drug development process of which it should become an integral part as early as possible. New insights derived from systems biology and systems pharmacology may give rise to exciting new opportunities of rational drug combinations, which can only be developed through the appropriate application of dynamical systems-based PK/PD models. It may well be that a new era of "systems therapeutics" will subsequently evolve.

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