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THE INTEGRATION OF PHARMACOKINETICS AND PHARMACODYNAMICS: Understanding Dose-Response

Susan M. Abdel-Rahman and Ralph E. Kauffman
Division of Pediatric Clinical Pharmacology and Medical Toxicology, The Children's Mercy Hospital and Clinics, Department of Pediatrics, University of Missouri-Kansas City, Kansas City, Missouri 64108; email: srahman@cmh.edu, rkauffman@cmh.edu

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■ **Abstract** Pharmacokinetic (PK) and pharmacodynamic (PD) studies have proven to be powerful and instructive tools, particularly in elucidating important aspects of human pharmacology. Nevertheless, they remain imperfect tools in that they only allow researchers to indirectly extrapolate, through computational modeling, the dynamic processes of drug action. Furthermore, neither tool alone provides a complete nor necessarily relevant picture of drug action. This review explores the utility and applications of PK and PD in the study of drugs, provides examples of lessons learned from their application to studies of human pharmacology, points out some of their limitations, and advances the thesis that these tools ideally should be employed together in an integrated approach. As we continue to apply these tools across the continuum of age and disease, they provide a powerful means to enhance our understanding of drug action, drug interactions, and intrinsic host factors that influence pharmacologic response.

INTRODUCTION

Central to the field of pharmacology is an understanding of the link between the interaction of a drug with its molecular target and the cumulative effects of this interaction on the cell, the organ system, or the intact organism. Several fundamental determinants guide pharmacologic response: (*a*) The physiochemical properties of the drug and biological properties of the tissues at the site of drug administration dictate the rate and extent to which the drug can enter the body. (*b*) The biochemical properties and metabolic capacity of the local environments through which the drug must traverse determine the rate and degree to which the drug can reach the site of action. (*c*) The genetic constitution of the host at the level of the receptor may influence the dynamics of the interaction between the drug and its target. (*d*) Finally, the pathophysiologic nature of the host may modulate postreceptor events initiated by the drug-receptor interaction, thereby influencing the quality,

time course, and intensity of the pharmacologic effect. Clearly, profiling the aggregate of these determinants presents a daunting task when one attempts to define dynamic drug-target interactions in complex intact organisms, such as humans. Rarely, if ever, can the independent processes involved in drug translocation, accumulation, subcellular localization, and receptor signaling be directly observed or quantitated. This has lead to the development, over the past 40–50 years, of computational approaches that allow description and prediction of drug exposure in the intact organism [e.g., pharmacokinetics (PK)] and relation of exposure to the onset, intensity, and duration of drug action [e.g., pharmacodynamics (PD)].

PK and PD have proven to be powerful and instructive tools, particularly in elucidating important aspects of human pharmacology. Nevertheless, they remain imperfect tools in that they only allow researchers to indirectly extrapolate, through computational modeling, the dynamic processes of drug action. Furthermore, neither PK nor PD alone provides a complete or necessarily relevant picture of drug action. That is, PK assessment of a drug is relevant only to the extent that drug concentration or exposure can be related to the drug actions of interest. Likewise, PD analysis of a drug has limited utility unless it can be related to the concentration over time and total exposure profile of the drug in the recipient. This review explores the utility and applications of PK and PD as important tools in the study of drugs, provides examples of lessons learned from their application to studies of human pharmacology, and points out some of their limitations. Our intent is to highlight the independent and combined roles of both tools in the clinical application of pharmacology and the generation of knowledge, which ultimately enhances the practice of medicine. It is not the purpose of this review to serve as a technical overview of PK/PD computational or modeling approaches, which have been well reviewed elsewhere (1, 2).

For the clinician, the requisite knowledge of pharmacology must be framed in the context of the dose-response relationship so that he/she may rationally apply optimal pharmacotherapeutics for the prevention and treatment of disease. The concept that there exists a proportional relationship between dose and effect predates the complex understanding that we now ascribe to the multifaceted dynamic interaction between drug and host. Daries, in the late eighteenth century, was the first to advance the notion that PD response (i.e., the duration of mydriasis observed following belladonna administration) varied in direct proportion to the size of the dose (3). Subsequent pharmacologic investigations over the past century, which continue to the present day, have confirmed the presence of such a relationship for the majority of drugs. However, it is recognized that drug response is susceptible to discernible biological variability. Individuals receiving the same dose of a pharmacologic agent may demonstrate responses that vary widely in onset, magnitude, and duration. It is this interindividual variability that presents the clinician with the greatest challenge when using a potent drug in the general population.

With the development of analytical techniques, which allow for the quantitation of active drug components in body fluids, and powerful computing tools to analyze the dynamics of drug concentration and effect, pharmacologists have the

tools to gain a better understanding of the variability in concentration-response by dissecting the relationship into its component dose-concentration (PK) and concentration-response (PD) elements. The following sections examine the application of PK and PD individually and together.

PHARMACOKINETIC APPLICATIONS

When considering the dose-response relationship in the organism, PK offers, in the place of dose, a concentration profile, which provides a more accurate estimate of the amount of drug that is available to enter the tissues and, thus, interact with the host at the level of the receptor. The resultant concentration or exposure profile for a given drug administered at a given dose provides a more suitable surrogate to explain interindividual variability in response than does dose alone. Well-conducted PK investigations afford the ability not only to describe the relationship between dose and concentration but to define the impact of intrinsic factors (i.e., those inherent to the recipient) and extrinsic factors (i.e., those external to the recipient) on the interindividual variability observed in drug biodisposition.

Intrinsic Factors

Many of the intrinsic factors that influence the relationship between dose and exposure are obvious and predictable based on recognized physiology. In these cases, PK has served to validate the overall contribution of these factors to the exposure profile following drug administration and to point the way to more targeted mechanistic research. The influence of ontogeny on drug biodisposition serves to illustrate this point. Major changes in organ size and function occur during normal growth and development that affect drug disposition. For example, information on structural renal development (i.e., the distribution of intrarenal blood flow, the recruitment of functional nephrons, and acquisition of active tubular transport mechanisms) that occurs during the first few months of life contributes to a well-characterized pattern for the acquisition of functional renal activity (i.e., glomerular filtration rate, para-amino-hippurate clearance) during postnatal development (4–6). As such, the clearance and, thus, resultant plasma concentrations relative to dose for compounds whose elimination is dependent on passive and active renal elimination show a clear relationship with age (7, 8). As a result of numerous PK evaluations validating the effect of alterations in renal physiology on drug clearance, the exposure profile of virtually any drug subject to renal elimination can largely be predicted a priori by considering (*a*) the sum contribution of active and passive renal processes on renal excretion of the drug, (*b*) the percentage of a given dose excreted unchanged in the urine, and (*c*) the influence of the intrinsic factor in question (e.g., age, senescence, disease) on renal function relative to that of a normal healthy adult (9).

Some intrinsic host factors are physiologically well defined, but the impact on drug disposition is not readily apparent because either relatively few drugs are

susceptible to the biological process in question or because the intrinsic influence is only apparent when combined with extrinsic factors, such as unique formulation characteristics. PK studies can serve to elucidate the influence of such intrinsic host factors that otherwise would go unappreciated. This can be illustrated by a recent series of PK studies evaluating a new antipicornaviral agent in which dose escalation in adults demonstrated a linear relationship between dose and exposure, whereas a one-step dose escalation in neonates unexpectedly produced neither an increase in maximum plasma concentration (Cmax) nor area-under-the-curve (AUC) (10, 11). The relatively lipophilic nature of the molecule combined with a formulation of medium-chain triglycerides to enhance solubility implied a role for intestinal lipase activity in regulating the absorption of this agent from its oral liquid preparation. A reevaluation of the literature on pediatric gastrointestinal physiology suggested that the extent of fat absorption in newborn infants varies, in part, owing to physiologically decreased intestinal lipolytic activity, with the lowest values observed early in the neonatal period (12–14). As such, the capacity-limited absorption observed in the antiviral PK study and earlier studies showing lipase-dependent absorption in premature newborns given similarly formulated antibiotics (15) provided PK support for the assertion that the dose-exposure profile for select drugs in neonates is modulated by normal, developmental gastrointestinal physiology. In contrast to the influence of renal development on drug exposure, both intrinsic (i.e., physiology) and extrinsic (i.e., formulation) factors were involved in determining drug biodisposition for these antiinfective agents such that their combined impact on the dose-exposure profile was only apparent a posteriori from carefully constructed and executed PK studies.

During the past decade, PK studies, combined with the development of molecular tools in the field of pharmacology, have allowed researchers to identify sources of intrinsic (e.g., genetic) variation in the host that are otherwise imperceptible yet clearly influence the dose-exposure relationship. Without phenotypic (i.e., PK) characterization, knowledge of this genetic variability would bear little relevance. For years, practitioners were aware that a small proportion of individuals demonstrated a unique susceptibility to the toxicity of many drugs (e.g., thiopurines, anesthetics, antiarrythmics, antihypertensives, anticoagulants) at doses normally tolerated by the majority of the population. PK evaluations served to confirm that drug and metabolite concentrations in the biological fluids of these subjects differed markedly from their "normal" counterparts and could explain much of the observed variability in clinical response (16–18). It was recognized that the traits governing the biodisposition of such agents were inherited (19), and subsequent advances in the field of molecular pharmacology and pharmacogenetics confirmed that the differences could be attributed to genetic polymorphisms. As a result of diligent efforts aimed at linking genetic variations with their pharmacokinetic phenotypic consequences, it is now possible in some instances to identify, prior to drug administration, patients in whom dose adjustment is necessary, thus mitigating toxic drug concentrations in these high-risk patients. Perhaps the most notable example of this approach, which has had the most immediate clinical impact,

involves thiopurine methyltransferase. By characterizing the phenotypic and genotypic expression of this drug-metabolizing enzyme in patients with leukemia, thiopurine doses less than 10% of those administered to the majority of the population are employed for the treatment of individuals who are homozygous for the enzyme mutation. Clearly, it would be impractical, if not impossible, to adjust the thiopurine dose empirically based solely on physiology, pathology, or demography in attempts to achieve the desired exposure profile. Knowledge of this genetic variation, combined with an understanding of its PK implications, allows appropriate dose adjustments to avoid undue toxicity (20, 21). Directed sequencing approaches remain ongoing in attempts to identify variations in the genes encoding the many proteins that regulate drug biodisposition. These molecular techniques are now being introduced into the design of PK trials earlier in the drug-development process by the pharmaceutical industry (22) with the aim of understanding and defining the variability nested in the dose-exposure relationship prior to seeking new drug approval or labeling changes. Such studies portend a future in which dosing of an increasing number of drugs will be tailored to the genetic characteristics of the individual patient.

As illustrated above, the clinician is better equipped to use a drug optimally when covariates that influence drug biodisposition pathways are recognized and when that knowledge is incorporated into the dosing guidelines for the drug. However, in many instances, the impact of select intrinsic factors on the dose-exposure relationship remains uncharacterized. PK evaluations reveal new aspects of human biology not previously described, and this leads to targeted mechanistic investigations. Knowledge elicited from PK trials originally designed to guide optimal dosing in a given patient population now serves as the driving force behind explorations aimed at further elucidation of the factors that regulate drug biotransformation. This is exemplified by the explosion of research in the area of drug metabolism. Most drugs are substrates for one or more of a host of cytochromes P450 and transferase enzymes that are responsible for catalyzing drug biotransformation, a critical determinant of systemic drug exposure. Again, studies on the ontogeny of drug metabolism serve as useful examples. During the past decade, much has been learned about the impact of normal growth and development on the acquisition of drug-metabolizing enzyme activity (23, 24). This follows many years during which PK studies suggested age-dependent maturation of drug elimination pathways. Indeed, PK studies continue to point the way to more basic studies of drug metabolism during maturation. A recent PK evaluation on the first agent in a new class of oxazolidinone antibiotics revealed that plasma clearance (65% of which was nonrenal, i.e., metabolic) increased rapidly after birth and exceeded adult values by nearly threefold after the first week of life (25). The implication of this finding on dose selection for an antibiotic agent where the exposure-effect relationship is clearly defined is obvious (26). Subsequent in vitro metabolic screens indicated that the drug was not a substrate for any of the major human cytochromes P450, and to date, the relevant biotransformation pathway remains incompletely characterized (27, 28). Beyond defining dose recommendations,

PK studies such as these play a critical role in identifying new areas of investigation in drug metabolism that otherwise might not be pursued.

Extrinsic Factors

PK studies also allow researchers to evaluate the influence of extrinsic factors, alone and in combination, on the dose-concentration relationship, independent of the patient. Pharmaceutical formulation is one critical extrinsic factor where product variability can markedly impact the dose-exposure relationship. This may be illustrated by the PK profile of a neuraminidase inhibitor delivered to influenza-challenged/infected patients, which revealed that an oral inhalation formulation provided exposure levels for the antiviral that were 160% greater than if delivered by intranasal spray and 230% greater than if delivered by intranasal drops. No covariates other than formulation contributed to the marked differences in relative bioavailability (29). In another example, modification of a parenteral anthracycline antineoplastic by encapsulating the drug within polyethylene glycol-coated liposomes strikingly altered the pharmacokinetic profile such that clearance was severely decreased and estimates of exposure increased by several orders of magnitude (30). The change in formulation directly influenced the drug's toxicity profile, which was reflected by a shift from leukopenia as the predominant adverse side effect to stomatitis and desquamating dermatitis (31). In contrast, a crossover PK study comparing an antipyretic formulated as both a suspension and effervescent granules revealed marked differences in the rate of absorption but no difference in the rate of onset and the extent of antipyretic effect (32).

In addition to formulation effects, PK investigations can help to identify and characterize clinically important drug-environment interactions. Interaction of therapeutic drugs with "alternative," "natural," or herbal preparations is currently attracting considerable attention. A number of examples are available that illustrate the importance of PK studies in understanding these interactions. The furanocoumarins, present in grapefruit juice, inhibit one of the most quantitatively important cytochromes P450 (CYP3A), primarily in the gut, and can increase the resultant systemic exposure profile for concurrently administered substrates of this enzyme with significant clinical implications (33–35). Hyperforin, an active component of the popular antidepressant herbal remedy St. John's wort, is capable of inducing both CYP3A and the transmembrane transport protein, P-glycoprotein, by activation of the nuclear receptor PXR (36). The effect is an increase in clearance and a decrease in systemic exposure of coadministered drugs that are substrates for these proteins. The magnitude of change expected in the dose-exposure profile for select medications varies depending on the relative contribution of CYP3A and P-glycoprotein to the overall biotransformation of the drug (37, 38). Similarly, the bioflavanoids present in apple juice have been shown to markedly reduce systemic exposure to agents from a number of drug classes, including the H_1- and H_2-receptor antagonists, immunosupressants, and mineral supplements (39–42). Although evidence exists for the inhibition of intestinal active drug transport

proteins (42), the mechanism of this interaction has not been fully elucidated. Without well-conducted PK studies, one could not predict with certainty for which substrates these interactions would be of clinical consequence.

In addition to nutritional factors and alternative therapies, PK investigations frequently are useful in evaluating the impact of environmental toxicants to which a host is exposed (or elects to consume) on the dose-exposure relationship of therapeutic agents. The polycyclic aromatic hydrocarbons present in tobacco smoke serve to illustrate this principle, having been well characterized as responsible for the induction of a number of drug-metabolizing enzymes (cytochromes P450 1A1, 1A2, and 2E1). An alteration in the PK profile, specifically an increase in drug clearance and resultant reduction in drug exposure, has been demonstrated in smokers for a number of pharmacologic agents, including bronchodilators, antidepressants, antihypertensives, muscle relaxants, antiarrythmics, antipsychotics, and hormone replacement agents (43). Interestingly, PK studies have shown that clearance rates in individuals exposed passively to cigarette smoke are also enhanced compared with nonsmokers (44). Cigarette smoking increases the clearance rates of theophylline by up to 80%, an effect that can persist for weeks to months after smoking cessation (45). For a drug with a relatively narrow therapeutic index, the impact of enhanced clearance and lower exposure profiles in smokers translates not only into an easily appreciated diminution in effect but also a similar reduction in toxicity. In fact, the incidence of theophylline toxicity is reduced by one half, from 13% to 7%, between nonsmokers and heavy-smokers (46). Although P450 induction is the most notable mechanism by which cigarette smoking can alter the dose-exposure profile of susceptible drugs, it is not the only mechanism. Cigarette smoking elicits numerous physiologic effects that can alter drug biodisposition, including cutaneous vasoconstriction with subsequent implications on the absorption of pharmacologic agents administered to the skin, as was observed for insulin (47, 48). However, recent data suggest that cigarette smoking may serve as a good example of where distinctions between the influence of extrinsic and intrinsic factors begin to blur. Epidemiologic data indicate that genetic variation may, in fact, determine cigarette consumption and vide inferre the degree to which an individual may clinically alter his/her dose-exposure profile for concurrently administered medications (49, 50).

Clinical Relevance

In addition to their research value, PK studies also have importance for the clinical practitioner. Data generated by PK studies arm the practitioners with a mechanism by which to refine their therapeutic decisions. Knowledge of the PK characteristics of a drug and the factors that contribute to variation in the drug's PK behavior affords the ability to control for the combination of intrinsic and extrinsic factors that can be expected to influence the dose-exposure profile for any given patient (as described above). PK data offer a means for comparison among agents within a class as it relates to rate and extent of exposure and thus onset, magnitude, and

duration of effect (51). Similarly, it allows the prescriber to evaluate if there is greater or lesser risk from nonadherence to dose instructions for agents within the same therapeutic class (52, 53). It affords the comparison of drug-interaction potential between agents within a class whether the knowledge is critical to avoid unintended consequences (e.g., prolonged QT interval with antihistamine/CYP3A-inhibitor combinations) or desirable to provide a health and/or economic benefit to the patient (e.g., antiretroviral combination interactions exploited to increase exposure and enhance efficacy) (54). Moreover, the confirmation of dose-exposure relationships by well-conducted PK investigations serves to validate the application of therapeutic drug monitoring and Bayesian forecasting in the clinical setting such that limited sampling schemes or single-point determinants of exposure can reliably verify the appropriateness of the dose selected (e.g., once daily aminoglycoside dosing nomograms), confirm that desired exposure targets are obtained (e.g., therapeutic concentrations of anticonvulsants, antipsychotics, antiarrhythmics, immunosupressants), and influence the decision to treat in the face of toxicity (e.g., Rumack-Matthew nomogram in acetaminophen overdose) (55–58). By defining the factors that contribute to interindividual variation in the dose-exposure relationship, the knowledge generated by PK investigations provides an alternative to traditional empiric dose adjustment and offers a means to more closely approach an optimal dosing regimen a priori for an individual or population.

PHARMACOKINETIC LIMITATIONS

Despite the broad utility of PK, a number of limitations must be acknowledged. Ideally, one would like to know the time course of drug concentration at the site of action. However, the majority of PK models are based on total drug concentration measured in plasma, not because plasma is the site of action, but primarily because it is the "tissue" most readily accessible for repeated sampling. An inherent assumption with models based on plasma or whole-blood concentrations is that, at steady state, there is a pseudoequilibrium between total drug and free drug concentration in plasma and between free drug concentrations in plasma and tissue. Consequently, it is necessary to attempt to extrapolate drug concentration in plasma to concentration at the site of action. There are, however, a number of circumstances where plasma drug concentrations may not reflect those present in the tissue of interest (59). Factors such as disease (e.g., trauma, malignancy, end-organ failure), concurrent medication use, pregnancy, and age can influence the affinity and capacity for drug binding to plasma and tissue proteins in a dynamic fashion (60–62). The properties of the capillary bed feeding the tissue, such as capillary density, tight junctions, and fenestrations, can be influenced by factors such as age and disease (e.g., atherosclerosis, diabetes). These properties regulate the extent of drug penetration and the rate at which a specific tissue reaches equilibrium with the plasma. For tissues where drug entry is restricted to transcellular

transport across the lipid bilayer, drug penetration and retention are governed by the lipid-water partition coefficient, the ionization rate constant of the drug, extracellular and intracellular pH, and the presence of active cellular transporters at the interface between plasma and tissue (63, 64). Finally, the physicochemical distribution of an intact drug within a particular physiologic fluid or compartment can serve to localize the drug to a specific tissue (65, 66). To the extent that the implicit assumptions do not hold, the mathematical models designed to extrapolate drug concentration in plasma to that at the site of action fail.

Another important consideration is that the total drug concentration measured in the biological fluid may not reflect the concentration of the active moiety. A notable example is seen with drugs that are given as a chiral mixture, where stereoselective biodisposition may occur such that the relative abundance of the respective enantiomers at any given time is changing but the change is not reflected by total drug concentration. For example, disopyramide demonstrates stereoselective, concentration-dependent binding within the therapeutic range with the free fraction of (R)-(−)-disopyramide nearly twofold greater than its stereoisomer. Moreover, renal and nonrenal clearance for (S)-(+)-disopyramide appears to be greater despite a similar affinity and capacity for both enantiomers with their shared metabolic pathway (CYP3A4). Not surprisingly, each enantiomer demonstrates unique electrophysiologic effects (67–70), which results in a dynamic profile of biological activity at the level of the receptor. The genotypic and phenotypic constitution of the host may further confound stereoselective biodisposition because genetically determined or pharmacologically mediated alterations in drug-metabolizing enzyme activity can selectively influence the disposition of a single enantiomer (71, 72). Similarly, age and gender have been shown to influence stereoselective biotransformation (73, 74).

Finally, PK is subject to the limitations inherent in the application of mathematical modeling techniques to any complex system. Information on drug movement in the body is subject to computational logic whereby a complex set of physiologic processes is distilled into a set of relatively simple mathematical equations. From these equations, we interpolate and/or extrapolate to make predictions on the behavior of the same or similar drugs in a wide range of patients and patient populations. Yet, we may neglect to appreciate the "regions of validity" beyond which predictions become imprecise, inaccurate, or frankly misleading. With the ease afforded by expanded computing capabilities, we may be tempted to apply models of unnecessary complexity to our dataset and thus define our systems of interest with models that lack biologic plausibility. Models may be enlisted to describe the average behavior of a drug in a population, yet the mean model parameters, as a measure of central tendency, may not be reflective of any single individual that makes up the model, and it may not accurately reflect the degree of interindividual variability nested in the parameter estimates. The prudent application of PK data requires an appreciation that the model is an abstraction of the essential determinants of drug movement, rather than a precise wholly descriptive means to define drug biodisposition.

PHARMACODYNAMIC APPLICATIONS

Whereas the underlying premise in PK is that a concentration-response relationship has been or can be defined, PD extends the analytical description of the dose-response relationship by attempting to describe the pharmacologic effect relative to concentration. PD makes the drug concentration profile derived from PK analysis biologically and pharmacologically relevant by completing the link between dose and effect. Thus, the research and clinical applications of PD are, for the most part, analogous to those described for PK.

Intrinsic Factors

The intrinsic factors, such as gender, age, race, and disease, that influence the dose-exposure relationship can independently influence response, and may, in fact, account for a greater proportion of the interindividual variability observed in the dose-response relationship (75). A principal application of PD studies is to reveal the impact of identifiable demographic, physiologic, and pathologic variables on the exposure-effect relationship. This is illustrated by several selected examples. Gender played a significant role in a PD study of a monoamine oxidase inhibitor, which revealed that the adverse event rates were more frequent in females than males, independent of exposure level (76). Age-dependent PD variation was described in the study of a skeletal muscle relaxant in which limited differences in the PK parameter estimates could be described, yet a delay in the onset of effect in elderly subjects compared with young subjects, defined by a slower rate of drug equilibration (i.e., smaller k_{e0}) into the biophase, was observed (77). Similarly, a more favorable antipyretic PD profile (e.g., earlier onset, greater magnitude, and longer duration of effect) was observed for infants compared with older children, despite a nonsteroidal antiinflammatory (NSAID) PK profile whose parameter estimates were independent of age (78). PD variation also may exist among different ethnic groups in the absence of pharmacokinetic differences. Significantly lower exposure levels of β-adrenergic receptor antagonists were required in Chinese subjects to produce the same magnitude of reduction in heart rate and blood pressure observed in Caucasian-American subjects despite no apparent difference in β-receptor density or affinity between the groups (79). In contrast, African-American subjects were less sensitive to the effects of the same β-blocker (80). Finally, disease also can influence PD response. PD evaluation of a thromboxane-receptor antagonist in patients with asthma identified that the slope of the concentration-effect relationship was heavily influenced by the severity of the underlying disease (81). The application of these relevant PD data to entire populations is increasingly more common and can be seen in the thoughtful discussion of intrinsic factors, such as race, gender, and age, in the publication of national treatment guidelines (82).

Although the physiological and molecular bases for variability in dose-response between individuals or populations may not be fully elucidated, many of the determinants that influence the exposure-response relationship can be attributed

to the underlying genetic constitution. Genetic polymorphisms have been characterized for genes encoding cytokines, estrogen receptors, β-adrenergic receptors, angiotensin-converting enzyme, and G proteins, among others, all of which modulate response to drug therapy independent of dose and exposure levels (83–86). Moreover, just as genetic variation in a single drug-metabolizing enzyme may be responsible for altered biotransformation of a number of substrates, genetic variability in a single receptor can influence host response to a number of substrates. Emerging data on sequence variations in the endothelial nitric oxide synthase (eNOS) gene illustrate this well. eNOS is expressed in the vascular endothelium and is responsible for synthesizing nitric oxide constitutively and in response to chemical or mechanical stimulation (87). Nitric oxide stimulates relaxation of the vascular smooth muscle and plays a role in hemodynamic status. Thus, changes in gene sequence, which translate into change in functional responsiveness of this receptor toward a pharmacologic substrate, would be expected to translate into variable PD response. A nucleotide transversion (G > T) in exon 7 of eNOS confers a Glu > Asp amino acid change in the protein. Not only is the mutation associated with cardiovascular disease (88) but also PD studies confirm that it is also associated with changes in the exposure-response relationship to several different classes of drugs. The presence of the mutation increased response to α-adrenergic stimulation in patients undergoing cardiac surgery, as measured by an increase in mean arterial pressure. The dose-response curve markedly shifted to the left in patients who were heterozygous for the mutation and shifted even further to the left in patients homozygous for the mutation (89). The same mutation significantly increased estradiol-stimulated platelet aggregation compared with individuals lacking the mutation, which suggests a role in the thrombotic response observed with these hormones (90). Further, individuals with the mutation were more likely to be poorly controlled in response to antihypertensive therapy (91). Studies that capture data that reflect the degree to which genetic variations can modulate PD drug response are of increasing interest. As methods by which a patient can be genotyped become mainstream, these data will be critical for optimizing drug therapy where rapid single-point determinants of exposure do not provide the necessary insight.

Extrinsic Factors

As is the case with PK, PD investigations can also be used to understand the role of extrinsic factors on host response. Establishing bioequivalence between formulations, routes of administration, and product manufacturers is another area where PD studies may be important. Although the evaluation of formulation effects and estimation of bioequivalence is often relegated to PK investigations, PD evaluations can be effectively used to compare responses between formulations. This is a particularly useful application when systemic drug concentrations are difficult to measure or are unavailable, as with topically applied drugs. Both safety (serum electrolytes, glucose, vital signs, and electrocardiogram) and efficacy (impact on FEV_1 in response to methcholine challenge) were evaluated and

verified to be comparable in a PD study designed to determine the bioequivalence of two inhaled long-acting β2-receptor antagonist formulations (92). In the absence of a commercially available product, where controls on the uniformity of product potency exist, PD can be used to ensure that extemporaneously compounded formulations demonstrate the same effect as the innovator product. Serial PD measurements over 12 h confirmed that the change in urine volume and urine osmolality were equivalent for several extemporaneous oral formulations of a synthetic vasopressin analog available only in tablet form. The authors subjected the area-under-the-effect-curve (analog of the PK AUC) and Emax (analog of the PK Cmax) to the FDA criteria for establishing bioequivalence, and in doing so, offered the practitioner useful data on the flexibility in medication administration for their patients who are unable to swallow whole tablets (93). PD bioequivalence studies are also useful to compare formulation effects during drug development when evaluation of PK bioequivalence in a bridging study is not suitable because the reference agent does not have an indication for the response of interest. A NSAID agent lacking an indication for pain because of its protracted absorption profile and delayed onset to analgesia was compared with a β-cyclodextrin complexed formulation. The investigation revealed that the modified formulation resulted in an earlier onset of pain relief, which coupled with a comparable extended duration of action owing to the inherent long half-life of the drug, provided a formulation with the desired PD profile (94). As illustrated, PD investigations afford a suitable surrogate for the evaluation of extrinsic factors when PK are met with restrictions.

PD studies provide evidence that environmental exposures can influence drug action in the same manner as they influence drug biodisposition. Among the more well-known examples in medicine is the interaction between warfarin and vitamin K. Patients consuming large amounts of vitamin K in their diet present with lower international normalized ratio (INR) values and require larger maintenance doses of warfarin to maintain their INR within the target range (95). Exposure to nicotine can also explain a variable dose-response relationship in the absence of changes in the dose-exposure-profile. An increase in the level of circulating catecholamines experienced by cigarette smokers blunts the magnitude of blood pressure and heart rate reduction in response to treatment with β-blockers. The stimulant effects of nicotine reduce the sedation observed with anxiolytics and the analgesia elicited by select opiates (96, 97). The absence of exposure to extrinsic factors can similarly impact PD response. Pharmacologic agents designed to increase bone mass may be less effective with inadequate intake of calcium, phosphorus, and vitamin D (98). As a result of PD investigations targeted at characterizing the impact of extrinsic factors on drug response, the rational modification of drug therapies or dosing regimens can be accomplished a priori in a number of circumstances.

Clinical Relevance

Clinically, PD investigations support the rational application for decisions related to the selection of dose and dosage regimen. A dose escalation study of a leutenizing

hormone-releasing hormone (LHRH) antagonist used to control ovulation provided a PD model that could be used to determine the dosing level necessary to produce the desired degree of LH suppression and identify the number of days required for the subsequent shift in the LH surge; a valuable economic benefit, given the cost associated with in vitro fertilization and the consequences associated with the retrieval of immature follicles with premature ovulation (99). Other studies have evaluated the systemic exposure profile of nicotine in association with cravings and determined which method(s) of nicotine replacement are likely to be the most effective in abolishing cravings (100). Such studies can be helpful in differentiating between drugs within a class (101); evaluating the nature, magnitude, and clinical significance of drug-drug interactions (102, 103); and validating the use of single point estimates of exposure to discriminate the likelihood of developing toxicity following an acute drug overdose, as with the acetaminophen toxicity nomogram (57, 104).

PHARMACODYNAMIC LIMITATIONS

As with PK approaches, PD methods also are subject to a number of limitations. PD characterization of a drug can be complicated by a number of factors, including lack of an obvious exposure-effect relationship, changes in PD behavior of the drug over time or in the presence of a progressive disease, and difficulty with accuracy or specificity in endpoint measurements.

In the vast majority of cases, it is not possible to evaluate concentrations at the level of the receptor, and the surrogate concentrations measured in readily accessible fluids may not accurately reflect the availability of active drug at the biophase. The amount of drug available to interact with the receptor may be restricted by local metabolism and transport at the tissue level (105, 106). The combination of parent and metabolite(s) may contribute to PD response (107). Further, the active metabolite may have a different time course and magnitude of effect than does the parent drug (108). Stereoselective interactions with the receptor may not be fully appreciated by evaluating the exposure-effect relationship, and response often does not reflect the aggregate activity of the individual enantiomers (109–111). Further, enantiomers may undergo chiral inversion in vivo (112). PD relationships described after single- or multiple-dose administration may not reflect the concentration of the drug available to interact with the receptor at steady state (113). Finally, factors such as concurrent medication use, comorbid conditions, and aging can displace a drug from its receptor site, not only moving the patient along the exposure-response curve but, at times, shifting the entire exposure-response relationship to the left or right (114, 115).

Change in receptor number, affinity, or transduction occurs with continued dosing of some drugs, leading to tolerance, thereby altering the measured response over time in the face of fixed exposure levels. The development of tolerance can have a dramatic effect on the exposure-response relationship and, if not recognized,

can complicate or confuse PD assessment of a drug. For example, the IC_{50} of an H_2-receptor antagonist doubled after prolonged exposure to the drug despite a relatively constant PK profile. This helped explain therapeutic unresponsiveness to the drug in the presence of constant fixed doses (116, 117). Further, the rate at which tolerance developed to the H_2-antagonist appeared to be a function of the method of drug administration and the severity of hyperacidity in the subject (116, 118). For some drugs, the rate at which tolerance develops can also vary as a function of the agent selected, even within a class of agents with similar chemical structure and mechanism of action. This may be related, in part, to differences in receptor affinity, occupancy, and duration of action of the drug. Such differences are illustrated by disparity in development of tolerance among the μ-receptor opiates and loop diuretics (119–121). These physiologic phenomena must be carefully considered when evaluating PD data generated under fixed conditions.

Plasma concentrations may be on the extremes of the sigmoidal exposure-response relationship, such that a relationship cannot be fully appreciated or the exposure-response may not adequately be defined by the standard (e.g., linear, log linear, sigmoidal) curve fit. Antimicrobials provide a good example of drugs where increasing concentration does not guarantee an increase in activity to some maximal effect where activity reaches a plateau. A number of antibiotics demonstrate a paradoxical reduction in antimicrobial activity with an increase in drug concentrations above those eliciting maximal effects (122, 123). Several mechanisms have been proposed to explain these observations, including induction of drug-degrading enzymes, dysregulation of the bacterial autolytic system, and secondary alterations in cellular functions that are requisite for antimicrobial activity with antibiotics that demonstrate polyfunctional activity (124–126). Similarly, exposure to subtherapeutic antimicrobial concentrations (as a result of underdosing, poor compliance, or a PK profile of the agent in question not affording adequate penetration to the site of infection) can manifest with variable effects depending on the organism and agent involved. Further, the effects are not simply a milder extension of those observed at inhibitory concentrations (i.e., movement along a single exposure-response curve) but, rather, represent effects that are qualitatively different from those observed when concentrations equal or exceed the minimum inhibitory concentration for the drug (127, 128).

Finally, it is difficult to develop outcome measures for some therapeutic areas that are sufficiently specific, accurate, and sensitive to conduct rigorous PD studies. For example, outcome variables, such as pain to assess analgesics and psychometric measures to assess antidepressants and antipsychotics, are highly subjective, making precise pharmacodynamic assessment challenging at best. Even well-accepted outcome measures do not always demonstrate 100% specificity. Select examples include the increase in cardiovascular risk observed with select short-acting dihydropyridine calcium-channel antagonists, despite the reduction in blood pressure (129), and the higher rate of death from arrhythmia in patients with symptomatic ventricular arrhythmia, despite the ability of select antiarrythmic agents to suppress premature ventricular contractions (130).

In some instances, the methods by which response variables are collected, or the variables themselves, may inaccurately or incompletely describe the PD relationship. For example, a study designed to establish the magnitude of interindividual variability in PD parameter estimates during antihypertensive therapy determined that manual blood pressure measurements, as opposed to ambulatory pressure monitoring, did not provide a sufficient density of data to address the question, largely because the practical constraints involved with manual monitoring did not allow the authors to account for circadian rhythms in blood pressure (131).

For some drugs, such as hypolipidemic agents, the outcome of interest, e.g., death due to atherosclerotic heart disease, is so far temporally removed that it is an impractical PD measure. In such cases, surrogate outcome measures, in this example reduction in serum lipids, must be employed. In lieu of measuring the definitive clinical response to therapy, surrogate biomarkers, such as erythrocyte-sedimentation rate in chronic infections or prostate-specific antigen in the management of prostate disease, are often employed; physiologic response variables, such as pupillary responsiveness with opiate administration, are measured; or physicomechanical measures, such as FEV_1 and exercise tolerance in asthma and stable angina, are used. A potential weakness of all surrogate endpoints is the implicit assumption that there is a predictive link between the surrogate and the definitive outcome. Unless this assumption is validated with acceptable confidence, the surrogate measure may not provide a true representation of PD response (132).

THE INTEGRATION OF PHARMACOKINETICS/ PHARMACODYNAMICS

PK and PD methods are powerful tools to describe and understand drug action in the intact organism. These tools are especially useful in human pharmacology, where studies of drug biodisposition and action must be relatively noninvasive and acceptably safe. Each provides a unique window on the pharmacologic behavior of the drug in the recipient. However, when applied in isolation, they provide an incomplete picture that limits their research-related and clinical relevance. The integrated application of PK and PD markedly enhances the power and utility of these tools by bridging the independent sets of information and negating the need to assume a relationship between dose and concentration or concentration and effect, as is inherent in the application of each tool alone.

Integration of the methods can be used to verify that plasma PK are a suitable surrogate for tissue PD in early drug development (133). In combination with diagnostic imaging techniques and radio-labeled drug, PK/PD investigations can validate the direct relationship between calculated PK parameter estimates and local tissue delivery of drug (134). The integrated approach can be used to distinguish the impact of placebo on overall response and, in some cases, confirm a physiologic mechanism for the placebo response; for example, release of endogenous

neurotransmitter (135). Integrated PK/PD studies can be used to determine the influence of disease on the combined disposition and response profile, evaluating the duration and magnitude of both exposure and effect relative to disease severity (136). Such studies can also provide insight into human physiology. This is illustrated by PK/PD studies of a humanized clotting factor, which provided a fuller understanding of the relationship between exogenously administered and endogenously synthesized proteins, thereby providing a model by which to understand the rates of formation and circulation of host proteins (137).

Concurrent evaluation of the dose-exposure and exposure-response relationships for outcomes of interest is highly useful in the development of a new drug. These relationships can be modeled early in new drug development and applied prospectively to enhance safety and efficiency of late-phase clinical studies. For example, in a combined PK/PD study of an investigational S-adenosylmethionine decarboxylase inhibitor, data pooled from three studies with multiple dosing regimens allowed the investigators to identify the single PK parameter that served as the most sensitive predictor of neutrophil count nadir and percent reduction in neutrophil count in response to treatment (138). These data were subsequently used to select the dosing regimen with the least likelihood of toxicity for subsequent clinical trials. With enough data to establish such a correlation, the same approach can also be used prospectively to predict response in a clinical setting with limited sampling schemes. In a similar investigation, a model was developed and validated to predict the total body exposure of an anthracycline antineoplastic drug from a single-point concentration measurement. The calculated exposure estimate was then used to predict leukocyte nadir after administration of the drug (139). In both studies, the correlation between predicted parameters and the outcome of interest (in these cases toxicity) ranged from 0.6–0.7. Although this indicates that a modest proportion of the variability in the dose-response relationship remains unaccounted for, the PK/PD models afford the investigator and clinician an option by which to minimize the risk of exposure-associated adverse events by a more palatable means than empiric dose adjustment.

For drugs whose application results in multiple pharmacologic/physiologic effects, the integration of PK and PD can distinguish the independent exposure-response relationships for the effects of interest. For example, by comparing several PK/PD parameter estimates, it was possible to discriminate the time course and magnitude of exposure required to produce the psychomotor and amnesic effects of benzodiazepines (140). PK/PD studies may be used to identify the dose and route of administration required for the same agent to elicit different exposure and subsequently different response profiles. This approach was used to study the different magnitudes and durations of suppression for two different endogenous hormones (e.g., LH and testosterone) in response to administration of the same synthetic antagonist (141). PK/PD studies also may be used to delineate the influence of food effects on the exposure profile of a drug. In this study, the food-drug interaction of a unique formulation of a dihydropyridine calcium channel blocker was characterized and subsequently used to predict the magnitude of change not

only in therapeutic outcome variables (e.g., blood pressure, heart rate) but also nondesirable outcomes (e.g., orthostasis, HA, flushing) (142).

Once established, the PK/PD relationships can offer insight into multifaceted drug-drug interactions. The management of human immunodeficiency virus infections relies heavily on PK/PD data to exploit drug-drug interactions for the benefit of the patient by engaging in or avoiding combinations of agents that can influence both exposure and virologic response rates (143–145). Further, they afford the clinician the ability to evaluate and anticipate the impact of drug-drug interactions on drug disposition and action when coadministration cannot be avoided, as in the case of refractory seizure disorders (146).

As was discussed in the sections on Limitations above, static determinations of PK/PD relationships cannot be expected to provide all of the insight that the clinician eventually needs in relation to optimizing drug therapy. The challenge of the patient where disease and disposition are dynamic remains a real concern. This is perhaps best illustrated by the number of PK/PD studies of levodopa in the treatment of Parkinson's disease, which provide an eye-opening example as to how both processes change along a continuum as the patients and/or their disease develops. As Parkinson's disease progresses and patients continue to age; the rate of drug transfer into and out of the effect site decreases, the duration of response to therapy is shorter, the magnitude of effect is smaller, the concentrations required to achieve 50% of maximal activity increases, the slope of the PK/PD curve becomes steeper, and the entire curve shifts to the right (147). Obviously, extrapolation of the combined PK/PD data derived from a set of patients at one stage in their disease will afford erroneous conclusions when applied to a set of patients in another stage.

CONCLUSIONS

PK and PD studies are powerful tools, when used correctly, to elucidate important aspects of human pharmacology. They serve to identify and understand sources of variability in dose-response, thereby minimizing uncertainty in prescribing decisions. These studies have broad research and clinical applications and have assumed increasing importance in academic research, for regulatory agencies, and in new drug development by the pharmaceutical industry. Although very useful, PK and PD studies, alone and in combination, are limited in that they provide an approximation of drug biodisposition and action based on mathematical modeling, which is only as good as the assumptions inherent in the model. Rational extrapolation from PK/PD data requires a comprehensive understanding of the system being modeled.

PK and PD are not mutually exclusive disciplines. Neither alone provides a complete characterization of the interaction between drug and recipient. Rather, they are complementary, each contributing a piece of the dose-response picture. Clearly, the greatest information regarding the pharmacology of a drug in the intact individual is gained by integrating applicable PK and PD approaches when possible. As we continue to learn how to apply these tools across the continuum

of age and disease, they provide a powerful means to enhance our understanding of drug effects, interactions between drugs, drug-environment interactions, and intrinsic host factors that influence response to drugs. This understanding can serve to identify focused areas of mechanistic research and as a "road map" to help the clinician address individual variation within the population, thereby ultimately enhancing care of the patient.

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LITERATURE CITED

1. Jusko W, Ko HC. 1994. Physiologic indirect response models characterize diverse types of pharmacodynamic effects. *Clin. Pharmacol. Ther.* 56:406–19
2. Holford NH, Sheiner LB. 1981. Pharmacokinetic and pharmacodynamic modeling in vivo. *CRC Crit. Rev. Biomed. Eng.* 5:273–322
3. Daries PJA. 1776. *De atropa belladonna.* Diss. Leipzig. Ex Off. Langenhemia, pp. 1–40
4. Robillard J, Guillery E, Petershack J. 1999. Renal function during fetal life. In *Pediatric Nephrology*, ed. TM Barratt, ED Avner, WE Harmon, pp. 21–37. Baltimore: Lippincott Williams & Wilkins
5. Arant BS Jr. 1978. Developmental patterns of renal functional maturation in the human neonate. *J. Pediatr.* 92:705–12
6. Papadopoulou ZL, Tina LU, Sandler P, Jose PA, Calcagno PL. 1978. Size and function of the kidneys. In *Children Are Different: Developmental Physiology*, ed. TR John, WM Moore, JE Jeffries, pp. 97–103. Columbus, OH: Ross Lab. 2nd ed.
7. Landers S, Berry PL, Kearns GL, Kaplan SL, Rudolph AJ. 1984. Gentamicin disposition and effect on development of renal function in the very low birth weight infant. *Dev. Pharmacol. Ther.* 7:285–302
8. Huisman-de Boer JJ, van den Anker JN, Vogel M, Goessens WH, Schoemaker RC, de Groot R. 1995. Amoxicillin pharmacokinetics in preterm infants with gestational ages of less than 32 weeks. *Antimicrob. Agents Chemother.* 39:431–34
9. Dettli L. 1976. Drug dosage in renal disease. *Clin. Pharmacokinet.* 1:126–34
10. Abdel-Rahman SM, Kearns GK. 1999. Single oral dose escalation pharmacokinetics of pleconaril (VP 63843) capsules in adults. *J. Clin. Pharmacol.* 39:613–18
11. Kearns GL, Bradley JS, Jacobs RF, Capparelli E, James LP, et al. 2000. Single-dose pharmacokinetics of pleconaril in neonates. *Pediatr. Infect. Dis. J.* 19:833–39
12. Filer LJ, Mattson FH, Fomon SJ. 1969. Triglyceride configuration and fat absorption by the human infant. *J. Nutr.* 99:293–98
13. Lee PC, Borysewicz R, Struve M, Raab K, Werlin SL. 1993. Development of lipolytic activity in gastric aspirates from premature infants. *J. Pediatr. Gastroenterol. Nutr.* 17:291–97
14. Hamosh M, Bitman J, Liao TH, Mehta NR, Buczek RJ, et al. 1989. Gastric lipolysis and fat absorption in preterm infants: effect of medium-chain triglyceride or long-chain triglyceride-containing formulas. *Pediatrics* 83:86–92
15. Shankaran S, Kauffman RE. 1984. Use of chloramphenicol palmitate in neonates. *J. Pediatr.* 105:113–16
16. Price Evans DA, Manley KA, McKusick VA. 1960. Genetic control of isoniazid metabolism in man. *Br. Med. J.* 2:485–91
17. Timbrell JA, Harland SJ, Facchini V.

1980. Polymorphic acetylation of hydralazine. *Clin. Pharmacol. Ther.* 28:350–55
18. Reidenberg MM, Drayer DE, Levy M, Warner H. 1975. Polymorphic acetylation of procainamide in man. *Clin. Pharmacol. Ther.* 17:722–30
19. Weinshilboum RM, Sladek SL. 1980. Mercaptopuine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. *Am. J. Hum. Genet.* 32:651–62
20. Krynetski EY, Tai HL, Yates CR, Fessing MY, Loennechen T, et al. 1996. Genetic polymorphism of thiopurine S-methyltransferase: clinical importance and molecular mechanisms. *Pharmacogenetics* 6:279–90
21. Otterness D, Szumlanski C, Lennard L, Klemetsdal B, Aarbakke J, et al. 1997. Human thiopurine methyltransferase pharmacogenetics: gene sequence polymorphisms. *Clin. Pharmacol. Ther.* 62:60–73
22. Kearns GL, Ferron G, James LP, Blumer JL, Gaedigk A, et al. 2003. Pantoprazole disposition in pediatrics. *Clin. Pharmacol. Ther.* 73:38 (Abstr.)
23. Hines RN, McCarver DG. 2002. The ontogeny of human drug-metabolizing enzymes: phase I oxidative enzymes. *J. Pharmacol. Exp. Ther.* 300:355–60
24. McCarver DG, Hines RN. 2002. The ontogeny of human drug metabolizing enzymes: phase II conjugation enzymes and regulatory mechanisms. *J. Pharmacol. Exp. Ther.* 300:361–66
25. Kearns GL, Abdel-Rahman SM, Blumer JL, Reed MD, James LP, et al. 2000. Single dose pharmacokinetics of linezolid in infants and children. *Pediatr. Infect. Dis. J.* 19:1178–84
26. Andes D, van Ogtrop ML, Peng J, Craig WA. 2002. In vivo pharmacodynamics of a new oxazolidinone (linezolid). *Antimicrob. Agents Chemother.* 46:3484–89
27. Slatter JG, Stalker DJ, Feenstra KL, Welshman IR, Bruss JB, et al. 2001. Pharmacokinetics, metabolism and excretion of linezolid following an oral dose of [(14)C] linezolid to healthy human subjects. *Drug Metab. Dispos.* 29:1136–45
28. Wynalda MA, Hauer MJ, Wienkers LC. 2000. Oxidation of the novel oxazolidinone antibiotic linezolid in human liver microsome. *Drug Metab. Dispos.* 28: 1014–17
29. Peng AW, Hussey EK, Moore KH. 2000. A population pharmacokinetic analysis of zanamivir in subjects with experimental and naturally occurring influenza: effects of formulation and route of administration. *J. Clin. Pharmacol.* 40:242–49
30. Gabizon A, Catane R, Uziely B, Kaufman B, Safra T, et al. 1994. Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. *Cancer Res.* 54:987–92
31. Uziely B, Jeffers S, Isacson R, Kutsch K, Wei-Tsao D, et al. 1995. Liposomal doxorubicin: antitumor activity and unique toxicities during two complementary phase I studies. *J. Clin. Oncol.* 13:1777–85
32. Troconiz IF, Armenteros S, Planelles MV, Benitez J, Calvo R, Dominguez R. 2000. Pharmacokinetic-pharmacodynamic modeling of the antipyretic effect of two oral formulations of ibuprofen. *Clin. Pharmacokinet.* 38:505–18
33. Guo LQ, Fukuda K, Ohta T, Yamazoe Y. 2000. Role of furanocoumarin derivatives on grapefruit juice-mediated inhibition of human CYP3A activity. *Drug Metab. Dispos.* 28:766–71
34. Andersen V, Pedersen N, Larsen NE, Sonne J, Larsen S. 2002. Intestinal first pass metabolism of midazolam in liver cirrhosis—effect of grapefruit juice. *Br. J. Clin. Pharmacol.* 54:120–24
35. Ho PC, Ghose K, Saville D, Wanwimolruk S. 2000. Effect of grapefruit juice on pharmacokinetics and pharmacodynamics of verapamil enantiomers in healthy volunteers. *Eur. J. Clin. Pharmacol.* 56:693–98
36. Moore LB, Goodwin B, Jones SA,

Wisely GB, Serabijt-Singh CJ, et al. 2000. St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. *Proc. Natl. Acad. Sci. USA* 97:7500–2

37. Mai I, Stormer E, Bauer S, Kruger H, Budde K, Roots I. 2003. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. *Nephrol. Dial. Transplant.* 18:819–22
38. Dresser GK, Schwarz UI, Wilkinson GR, Kim RB. 2003. Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. *Clin. Pharmacol. Ther.* 73:41–50
39. Abdel-Rahman SM, Johnson FK, Gauthier-Dubois G, Weston IE, Kearns GL. 2003. The bioequivalence of nizatidine (Axid®) in three extemporaneously and commercially prepared oral liquid formulations compared with capsule. *J. Clin. Pharmacol.* 43:148–53
40. FDA Talk Paper. 2000. *Nationwide Recall of SangCya Oral Solution*, TOO-32, July 10
41. Glahn RP, Lee OA, Miller DD. 1998. Application of an in vitro digestion/CACO-2 cell culture model to determine optimal ascorbic acid to iron ratio in commercial infant rice cereal. *Tektran USDA Agric. Res. Serv. Database* (*Abstr.*)
42. Dresser GK, Bailey DG, Leake BF, Schwarz UI, Dawson PA, et al. 2002. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral bioavilability of fexofenadine. *Clin. Pharmacol. Ther.* 71:11–20
43. Zevin S, Benowitz NL. 1999. Drug interactions with tobacco smoking. An update. *Clin. Pharmacokinet.* 36:425–38
44. Matsunga SK, Plezia PM, Karol MD, Katz MD, Camilli AE, Benowitz NL. 1989. Effects of passive smoking on theophylline clearance. *Clin. Pharmacol. Ther.* 46:399–407
45. Hunt SN, Jusko WJ, Yurchak AM. 1976. Effect of smoking on theophylline disposition. *Clin. Pharmacol. Ther.* 19:546–51
46. Pfeifer HJ, Greenblatt DJ. 1978. Clinical toxocity of theophylline in relation to cigarette smoking. A report from the Boston Collaborative Drug Surveillance Program. *Chest* 73:455–59
47. Benowitz NL, Jacob P III, Jones RT, Rosenberg J. 1982. Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. *J. Pharmacol. Exp. Ther.* 221:368–72
48. Klemp P, Staberg B, Madsbad S, Kolendorf K. 1982. Smoking reduces insulin absorption from subcutaneous tissue. *Br. Med. J.* 284:237
49. Sellers EM, Tyndale RF. 2000. Mimicking gene defects to treat drug dependence. *Ann. NY Acad. Sci.* 909:233–46
50. Tyndale RF, Pianezza ML, Sellers EM. 1999. A common genetic defect in nicotine metabolism decreases risk for dependence and lowers cigarette consumption. *Nicotine Tob. Res.* 1:S63–67
51. Csajka C, Buclin T, Fattinger K, Brunner HR, Biollaz J. 2002. Population pharmacokinetic-pharmacodynamic modeling of angiotensin receptor blockade in healthy volunteers. *Clin. Pharmacokinet.* 41:137–52
52. Dresser GK, Spence JD, Bailey DG. 2000. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin. Pharmacokinet.* 38:41–57
53. Boissel JP, Nony P. 2002. Using pharmacokinetic-pharmacodynamic relationships to predict the effect of poor compliance. *Clin. Pharmacokinet.* 41:1–6
54. Levy G, Zamacona MK, Jusko WJ. 2000. Developing compliance instructions for drug labeling. *Clin. Pharmacol. Ther.* 68:586–91
55. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. 1995. Experience with a once-daily aminoglycoside program administered to

2,184 adult patients. *Antimicrob. Agents Chemother.* 39:650–55
56. Eadie MJ. 1994. Plasma antiepileptic drug monitoring in a neurological practice: a 25-year experience. *Ther. Drug Monit.* 16: 458–68
57. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. 1988. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976–1985). *N. Engl. J. Med.* 319:1557–62
58. Schumacher GE, Barr JT. 1994. Bayesian and threshold probabilities in therapeutic drug monitoring: when can serum drug concentrations alter clinical decisions? *Am. J. Hosp. Pharm.* 51:321–27
59. Kawai R, Mathew D, Tanaka C, Rowland M. 1998. Physiologically based pharmacokinetics of cyclosporine A: extension to tissue distribution kinetics in rats and scale-up to human. *J. Pharmacol. Exp. Ther.* 287:457–68
60. Edwards DJ, Axelson JE, Slaughter RL, Elvin AT, Lalka D. 1984. Factors affecting quinidine protein binding in humans. *J. Pharm. Sci.* 73:1264–67
61. Mitani GM, Steinberg I, Lien EJ, Harrison EC, Elkayam U. 1987. The pharmacokinetics of antiarrhythmic agents in pregnancy and lactation. *Clin. Pharmacokinet.* 12:253–91
62. Windorfer A, Karitzky D, Gasteiger U, Stehr K. 1978. Investigations on salicylate protein binding in newborns and infants. *Eur. J. Pediatr.* 127:163–72
63. Tamai I, Tsuji A. 2000. Transporter-mediated permeation of drugs across the blood-brain barrier. *J. Pharm. Sci.* 89: 1371–88
64. Rao VV, Dahlheimer JL, Bardgett ME, Snyder AZ, Finch RA, et al. 1999. Choroid plexus epithelial expression of MDR1 P glycoprotein and multidrug resistance-associated protein contribute to the blood-cerebrospinal-fluid drug-permeability barrier. *Proc. Natl. Acad. Sci. USA* 96:3900–5
65. Walstad RA, Hellum KB, Blika S, Dale LG, Fredriksen T, et al. 1983. Pharmacokinetics and tissue penetration of ceftazidime: studies on lymph, aqueous humour, skin blister, cerebrospinal and pleural fluid. *J. Antimicrob. Chemother.* 12(Suppl. A):275–82
66. Gan VN, McCarty JM, Chu SY, Carr R. 1997. Penetration of clarithromycin into middle ear fluid of children with acute otitis media. *Pediatr. Infect. Dis. J.* 16:39–43
67. Valdivieso L, Giacomini KM, Nelson WL, Pershe R, Blaschke TF. 1988. Stereoselective binding of disopyramide to plasma proteins. *Pharm. Res.* 5:316–18
68. Le Corre P, Gibassier D, Sado P, Le Verge R. 1988. Stereoselective metabolism and pharmacokinetics of disopyramide enantiomers in humans. *Drug Metab. Dispos.* 16:858–64
69. Zhang L, Fitzloff JF, Engel LC, Cook CS. 2001. Species difference in stereoselective involvement of CYP3A in the mono-N-dealkylation of disopyramide. *Xenobiotica* 31:73–83
70. Lima JJ, Boudoulas H. 1987. Stereoselective effects of disopyramide enantiomers in humans. *J. Cardiovasc. Pharmacol.* 9: 594–600
71. Gross AS, Mikus G, Fischer C, Hertrampf R, Gundert-Remy U, Eichelbaum M. 1989. Stereoselective disposition of flecainide in relation to the sparteine/debrisoquine metaboliser phenotype. *Br. J. Clin. Pharmacol.* 28:555–66
72. Birgersdotter UM, Wong W, Turgeon J, Roden DM. 1992. Stereoselective genetically-determined interaction between chronic flecainide and quinidine in patients with arrhythmias. *Br. J. Clin. Pharmacol.* 33:275–80
73. Sutfin T, Balmer K, Bostrom H, Eriksson S, Hoglund P, Paulsen O. 1989. Stereoselective interaction of omeprazole with warfarin in healthy men. *Ther. Drug Monit.* 11:176–84
74. Gupta SK, Atkinson L, Tu T, Longstreth JA. 1995. Age and gender related changes

in stereoselective pharmacokinetics and pharmacodynamics of verapamil and norverapamil. *Br. J. Clin. Pharmacol.* 40: 325–31

75. Gobburu JV, Agerso H, Jusko WJ, Ynddal L. 1999. Pharmacokinetic-pharmacodynamic modeling of ipamorelin, a growth hormone releasing peptide, in human volunteers. *Pharm. Res.* 16:1412–16
76. Guentert TW, Banken L, Hilton S, Holford NH. 1995. Moclobemide: relationships between dose, drug concentration in plasma, and occurrence of adverse events. *J. Clin. Psychopharmacol.* 15(4 Suppl. 2):S84–94
77. Sorooshian SS, Stafford MA, Eastwood NB, Boyd AH, Hull CJ, Wright PM. 1996. Pharmacokinetics and pharmacodynamics of cisatracurium in young and elderly adult patients. *Anesthesiology* 84:1083–91
78. Kauffman RE, Nelson MV. 1992. Effect of age on ibuprofen pharmacokinetics and antipyresis response. *J. Pediatr.* 6:969–73
79. Zhou HH, Koshakji RP, Silberstein DJ, Wilkinson GR, Wood AJJ. 1989. Racial differences in drug response: altered sensitivity to and clearance of propranolol in men of Chinese descent as compared with American whites. *N. Engl. J. Med.* 320:560–70
80. Cubeddu LX, Aranda J, Singh B, Klein M, Brachfeld J, et al. 1986. A comparison of verapamil and propranolol for the initial treatment of hypertension. Racial differences in response. *JAMA* 256:2214–21
81. Samara E, Cao G, Locke C, Granneman GR, Dean R, Killian A. 1997. Population analysis of the pharmacokinetics and pharmacodynamics of seratrodast in patients with mild to moderate asthma. *Clin. Pharmacol. Ther.* 62:426–35
82. Natl. Inst. Health—Natl. Heart, Lung, and Blood Inst. 1997. *The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure*. NIH Publ. No. 98-4080, Nov.
83. Daly AK, Day CP, Donaldson PT. 2002. Polymorphisms in immunoregulatory genes: towards individualized immunosuppressive therapy? *Am. J. Pharmacogenomics* 2:13–23
84. Liggett SB. 2000. Pharmacogenetics of beta-1- and beta-2-adrenergic receptors. *Pharmacology* 61:167–73
85. Schwartz GL, Turner ST, Chapman AB, Boerwinkle E. 2002. Interacting effects of gender and genotype on blood pressure response to hydrochlorothiazide. *Kidney Int.* 62:1718–23
86. Turner ST, Schwartz GL, Chapman AB, Boerwinkle E. 2000. Racial differences in response to acute dosing with hydrochlorothiazide. *Am. J. Hypertens.* 13:157–64
87. Palmer RMJ, Ferrige AG, Moncada S. 1987. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 327:524–26
88. Yoshimura M, Yasue H, Nakayama M, Shimasaki Y, Sumida H, et al. 1998. A missense Glu298Asp variant in the endothelial nitric oxide synthase gene is associated with coronary spasm in the Japanese. *Hum. Genet.* 103:65–69
89. Philip I, Plantefeve G, Vuillaumier-Barrot S, Vicaut E, LeMarie C, et al. 1999. G894T polymorphism in the endothelial nitric oxide synthase gene is associated with an enhanced vascular responsiveness to phenylephrine. *Circulation* 99:3096–98
90. Tanus-Santos JE, Desai M, Deak LR, Pezzullo JC, Abernethy DR, et al. 2002. Effects of endothelial nitric oxide synthase gene polymorphisms on platelet function, nitric oxide release, and interactions with estradiol. *Pharmacogenetics* 12:407–13
91. Jachymova M, Horky K, Bultas J, Kozich V, Jindra A, et al. 2001. Association of the Glu298Asp polymorphism in the endothelial nitric oxide synthase gene with essential hypertension resistant to

conventional therapy. *Biochem. Biophys. Res. Commun.* 284:426–30
92. Marzo A, Monti NC, Tettamanti RA, Crivelli F, Dal Bo L, et al. 2000. Bioequivalence of inhaled formoterol fumarate assessed from pharmacodynamic, safety and urinary pharmacokinetic data. *Arzneim. Forsch.* 50:559–63
93. Argenti D, Ireland D, Heald DL. 2001. A pharmacokinetic and pharmacodynamic comparison of desmopressin administered as whole, chewed and crushed tablets, and as an oral solution. *J. Urol.* 165:1446–51
94. Wang D, Miller R, Zheng J, Hu CP. 2000. Comparative population pharmacokinetic-pharmacodynamic analysis for piroxicam-beta-cyclodextrin and piroxicam. *J. Clin. Pharmacol.* 40:1257–66
95. Lubetsky A, Dekel-Stern E, Chetrit A, Lubin F, Halkin H. 1999. Vitamin K intake and sensitivity to warfarin in patients consuming regular diets. *Thromb. Haemost.* 81:396–99
96. Zevin S, Benowitz NL. 1999. Drug interactions with tobacco smoking. An update. *Clin. Pharmacokinet.* 36:425–38
97. Buhler FR, Vesanen K, Watters JT, Bolli P. 1988. Impact of smoking on heart attacks, strokes, blood pressure control, drug dose, and quality of life aspects in the International Prospective Primary Prevention Study in Hypertension. *Am. Heart. J.* 115:282–88
98. Heaney RP. 2001. Constructive interactions among nutrients and bone-active pharmacologic agents with principal emphasis on calcium, phosphorus, vitamin D and protein. *J. Am. Coll. Nutr.* 20(5 Suppl.):S403–9
99. Nagaraja NV, Pechstein B, Erb K, Klipping C, Hermann R, et al. 2000. Pharmacokinetic and pharmacodynamic modeling of cetrorelix, an LH-RH antagonist, after subcutaneous administration in healthy premenopausal women. *Clin. Pharmacol. Ther.* 68:617–25
100. Gomeni R, Teneggi V, Iavarone L, Squassante L, Bye A. 2001. Population pharmacokinetic-pharmacodynamic model of craving in an enforced smoking cessation population: indirect response and probabilistic modeling. *Pharm. Res.* 18:537–43
101. Lemmens HJ, Dyck JB, Shafer SL, Stanski DR. 1994. Pharmacokinetic-pharmacodynamic modeling in drug development: application to the investigational opioid trefentanil. *Clin. Pharmacol. Ther.* 56:261–71
102. van den Berg BT, Derks MG, Koolen MG, Braat MC, Butter JJ, van Boxtel CJ. 1999. Pharmacokinetic/pharmacodynamic modeling of the eosinopenic and hypokalemic effects of formoterol and theophylline combination in healthy men. *Pulm. Pharmacol. Ther.* 12:185–92
103. Belani CP, Egorin MJ, Abrams JS, Hiponia D, Eisenberger M, et al. 1989. A novel pharmacodynamically based approach to dose optimization of carboplatin when used in combination with etoposide. *J. Clin. Oncol.* 7:1896–902
104. Rumack BH, Matthew H. 1975. Acetaminophen poisoning and toxicity. *Pediatrics* 55:871–76
105. Pennycooke M, Chaudary N, Shuralyova I, Zhang Y, Coe IR. 2001. Differential expression of human nucleoside transporters in normal and tumor tissue. *Biochem. Biophys. Res. Commun.* 280:951–59
106. Pelkonen O, Raunio H. 1997. Metabolic activation of toxins: tissue-specific expression and metabolism in target organs. *Environ. Health Perspect.* 105(Suppl. 4):767–74
107. Mandema JW, Tuk B, van Steveninck AL, Breimer DD, Cohen AF, Danhof M. 1992. Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteers. *Clin. Pharmacol. Ther.* 51: 715–28
108. Ragueneau I, Laveille C, Jochemsen R, Resplandy G, Funck-Brentano C,

Jaillon P. 1998. Pharmacokinetic-pharmacodynamic modeling of the effects of ivabradine, a direct sinus node inhibitor, on heart rate in healthy volunteers. *Clin. Pharmacol. Ther.* 64:192–203
109. Williams KM. 1989. Chirality: pharmacokinetics and pharmacodynamics in 3 dimensions. *Clin. Exp. Pharmacol. Physiol.* 16:465–70
110. Mehvar R, Brocks DR, Vakily M. 2002. Impact of stereoselectivity on the pharmacokinetics and pharmacodynamics of antiarrhythmic drugs. *Clin. Pharmacokinet.* 41:533–58
111. Jonkers RE, Koopmans RP, Portier EJ, van Boxtel CJ. 1991. Debrisoquine phenotype and the pharmacokinetics and beta-2 receptor pharmacodynamics of metoprolol and its enantiomers. *J. Pharmacol. Exp. Ther.* 256:959–66
112. Eriksson T, Bjorkman S, Roth B, Fyge A, Hoglund P. 1998. Enantiomers of thalidomide: blood distribution and the influence of serum albumin on chiral inversion and hydrolysis. *Chirality* 10:223–28
113. Schwartz JB, Verotta D, Sheiner LB. 1989. Pharmacodynamic modeling of verapamil effects under steady-state and nonsteady-state conditions. *J. Pharmacol. Exp. Ther.* 251:1032–38
114. Das G, Barr CE, Carlson J. 1984. Reduction of digoxin effect during the digoxin-quinidine interaction. *Clin. Pharmacol. Ther.* 35:317–21
115. Kubacka RT, Antal EJ, Juhl RP. 1987. The paradoxical effect of cimetidine and ranitidine on glibenclamide pharmacokinetics and pharmacodynamics. *Br. J. Clin. Pharmacol.* 23:743–51
116. Mathot RAA, Geus WP. 1999. Pharmacodynamic modeling of the acid inhibitory effect of ranitidine in patients in an intensive care unit during prolonged dosing: characterization of tolerance. *Clin. Pharmacol. Ther.* 66:140–51
117. Smith JT, Gavey C, Nwokolo CU, Pounder RE. 1990. Tolerance during 8 days of high-dose H2-blockade: placebo-controlled studies of 24-hour acidity and gastrin. *Aliment. Pharmacol. Ther.* 4(Suppl. 1):47–63
118. Wilder-Smith CH, Halter F, Merki HS. 1991. Tolerance and rebound to H2-receptor antagonists: intragastric acidity in patients with duodenal ulcer. *Dig. Dis. Sci.* 36:1685–90
119. Whistler JL, Chuang HH, Chu P, Jan LY, von Zastrow M. 1999. Functional dissociation of mu opioid receptor signaling and endocytosis: implications for the biology of opiate tolerance and addiction. *Neuron* 23:737–46
120. Brater DC. 2000. Pharmacology of diuretics. *Am. J. Med. Sci.* 319:38–50
121. Marshall JD, Well TG, Letzig L, Kearns GL. 1998. Pharmacokinetics and pharmacodynamics of bumetanide in critically ill pediatric patients. *J. Clin. Pharmacol.* 38:994–1002
122. Kirby WMM. 1945. Bacteriostatic and lytic actions of penicillin on sensitive and resistant staphylococci. *J. Clin. Invest.* 24: 165–69
123. Eagle H, Musselman AD. 1948. The rate of bactericidal action of penicillin in vitro as a function of its concentration, and its paradoxically reduced activity at high concentration against certain organisms. *J. Exp. Med.* 88:99–131
124. Ikeda Y, Nishino T. 1988. Paradoxical antibacterial activities of beta-lactams against Proteus vulgaris: mechanism of the paradoxical effect. *Antimicrob. Agents Chemother.* 32:1073–77
125. Fontana R, Boaretti M, Grossato A, Tonin EA, Lleo MM, Satta G. 1990. Paradoxical response of *Enterococcus faecalis* to the bactericidal activity of penicillin is associated with reduced activity of one autolysin. *Antimicrob. Agents Chemother.* 34:314–20
126. Ryffel C, Strassle A, Kayser FH, Berger-Bachi B. 1994. Mechanisms of heteroresistance in methicillin-resistant *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* 38:724–28

127. Lorian V. 1975. Some effects of subinhibitory concentrations of antibiotics on bacteria. *Bull. NY Acad. Med.* 51:1046–55
128. Tornqvist IO, Holm SE, Cars O. 1991. Pharmacodynamic effects of subinhibitory antibiotic concentrations. *Scand. J. Infect. Dis.* 74(Suppl.):94–101
129. Alderman MH, Cohen H, Roque R, Madhavan S. 1997. Effect of long-acting and short-acting calcium antagonists on cardiovascular outcomes in hypertensive patients. *Lancet* 349:594–98
130. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. 1989. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N. Engl. J. Med.* 321:406–12
131. Troconiz IF, de Alwis DP, Tillmann C, Callies S, Mitchell M, Schaefer HG. 2000. Comparison of manual versus ambulatory blood pressure measurements with pharmacokinetic-pharmacodynamic modeling of antihypertensive compounds: application to moxonidine. *Clin. Pharmacol. Ther.* 68:18–27
132. Rolan P. 1997. The contribution of clinical pharmacology surrogates and models to drug development—a critical appraisal. *Br. J. Clin. Pharmacol.* 44:219–25
133. Cutler NR, Polinsky RJ, Sramek JJ, Enz A, Jhee SS, et al. 1998. Dose-dependent CSF acetylcholinesterase inhibition by SDZ ENA 713 in Alzheimer's disease. *Acta Neurol. Scand.* 97:244–50
134. Dietz M, Harder S, Graff J, Kunig G, Vontobel P, et al. 2001. Levodopa pharmacokinetic-pharmacodynamic modeling and 6-[18F]levodopa positron emission tomography in patients with Parkinson's disease. *Clin. Pharmacol. Ther.* 70:33–41
135. de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, et al. 2001. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* 293:1164–66
136. Lapicque F, Vergne P, Jouzeau JY, Loeuille D, Gillet P, et al. 2000. Articular diffusion of meloxicam after a single oral dose: relationship to cyclo-oxygenase inhibition in synovial cells. *Clin. Pharmacokinet.* 39:369–82
137. Chow FS, Benincosa LJ, Sheth SB, Wilson D, Davis CB, et al. 2002. Pharmacokinetic and pharmacodynamic modeling of humanized anti-factor IX antibody (SB 249417) in humans. *Clin. Pharmacol. Ther.* 71:235–45
138. Zhou H, Choi L, Lau H, Bruntsch U, Vries EE, et al. 2000. Population pharmacokinetics/toxicodynamics (PK/TD) relationship of SAM486A in phase I studies in patients with advanced cancers. *J. Clin. Pharmacol.* 40:275–83
139. Leca FR, Marchiset-Leca D, Galeani A, Noble A, Catalin J. 1998. Pharmacokinetic-pharmacodynamic relationships between pirarubicin exposure and hematotoxicity: clinical application using only one blood sample. *Anticancer Drugs* 9: 503–9
140. Blin O, Simon N, Jouve E, Habib M, Gayraud D, et al. 2001. Pharmacokinetic and pharmacodynamic analysis of sedative and amnesic effects of lorazepam in healthy volunteers. *Neuropharmacology* 24:71–81
141. Pechstein B, Nagaraja NV, Hermann R, Romeis P, Locher M, Derendorf H. 2000. Pharmacokinetic-pharmacodynamic modeling of testosterone and luteinizing hormone suppression by cetrorelix in healthy volunteers. *J. Clin. Pharmacol.* 40:266–74
142. Schaefer HG, Heinig R, Ahr G, Adelmann H, Tetzloff W, Kuhlmann J. 1997. Pharmacokinetic-pharmacodynamic modelling as a tool to evaluate the clinical relevance of a drug-food interaction for a nisoldipine controlled-release dosage form. *Eur. J. Clin. Pharmacol.* 51:473–80

143. Hsu A, Isaacson J, Brun S, Bernstein B, Lam W, et al. 2003. Pharmacokinetic-pharmacodynamic analysis of lopinavir-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodeficiency virus-infected patients. *Antimicrob. Agents Chemother.* 47:350–59
144. Gerber JG. 2000. Using pharmacokinetics to optimize antiretroviral drug-drug interactions in the treatment of human immunodeficiency virus infection. *Clin. Infect. Dis.* 30(Suppl. 2):S123–29
145. van Heeswijk RP, Veldkamp A, Mulder JW, Meenhorst PL, Lange JM, et al. 2001. Combination of protease inhibitors for the treatment of HIV-1-infected patients: a review of pharmacokinetics and clinical experience. *Antivir. Ther.* 6:201–29
146. Patsalos PN, Froscher W, Pisani F, van Rijn CM. 2002. The importance of drug interactions in epilepsy therapy. *Epilepsia* 43:365–85
147. Harder S, Baas H, Rietbrock S. 1995. Concentration-effect relationship of levodopa in patients with Parkinson's disease. *Clin. Pharmacokinet.* 29:243–56