Introduction

Effective pharmacotherapy requires a correct diagnosis, selection of the right medication, and an appropriate drug dosage regimen. The latter is a function of the drug's pharmacokinetic and pharmacodynamic characteristics and the individual patient's physiologic status. There are pronounced interindividual differences in the relationship between drug dosage and the intensity of the pharmacologic response elicited by most drugs. This is due to pharmacokinetic variability, *i.e.*, variability in the relationship between dose and drug concentration in relevant body fluids (such as the blood plasma), as well as to variability in the relationship between drug concentration and intensity of drug action (pharmacodynamics). So far, most attention and research efforts have been focused on pharmacokinetics, whereas only relatively recently has significant attention been directed to pharmacodynamics. In fact, the magnitude of pharmacodynamic variability often exceeds that of pharmacokinetic variability[1, 2]. When a drug's therapeutic and adverse effects are mediated by different receptor systems, differential variability of both systems can result in pronounced interindividual variability in the therapeutic index of a drug[1].

The literature is often confusing or uncertain as to the cause of changes in the relationship between dose and therapeutic response. What is claimed to be a pharmacodynamic change is often entirely pharmacokinetic. In other cases, pharmacokinetic and pharmacodynamic perturbations occur concurrently. To distinguish between the two, careful attention must be directed to possible quantitative changes in a drug's plasma protein binding, distribution in the body and biotransformation (particularly with respect to changes in exposure to active metabolites). Thus, pharmacodynamic studies in humans and animals are usually much more difficult and technically demanding than pharmacokinetic investigations. The major problem in pharmacodynamic research is measurement methodology; pharmacologic effects are generally more difficult to measure than drug and drug metabolite concentrations.

The relationship between drug concentration in plasma and intensity of pharmacologic effect is often obscured by delays in effect relative to the time course of drug concentration (hysteresis), due either to the time required for distribution to the site of drug action or the existence of a reaction cascade[3], or because drug action is indirect[4,5]. Preclinical studies in animals can define the structural model of a drug's pharmacodynamics and thereby facilitate the design and interpretation of the results of clinical investigations.
In this context, pharmacologically effective drug concentrations in animals (particularly rodents) and humans are often quite similar[6]. The greater

invasiveness permitted in animal studies can also overcome certain distributional delays that may complicate clinical investigations. For example, it is possible to serially withdraw samples of cerebrospinal fluid from rats for drug concentration determinations and thereby bypass the blood-brain barrier. However, recent developments in microdialysis and imaging are extending significantly the scope of pharmacodynamic studies in humans.

Pharmacodynamic variability can be due to genetic or environmental causes and in most instances is due to both. Among the environmental causes are concomitant or preceding exposure to other drugs, age, gender, diet, and disease(s). Diseases can affect receptor density and/or affinity, alter the concentration of endogenous substances that interact with receptors, and modify transduction processes and homeostatic reactions. For example, a quantitative relationship between the pharmacodynamics of L-dopa and the severity of Parkinson's disease (Hoehn-Yahr classification) has been demonstrated[7].

The difference between pharmacokinetics and pharmacodynamics is not always distinct, particularly for drugs that are substrates of physiologic transporters. In a clinical setting, changes in the relationship between plasma concentration and effect intensity may be due to distributional changes caused by altered or unusual characteristics of a transporter system at the blood-brain barrier or at other functional barriers that separate a drug in fluids of distribution from its biophase. For example, the entry of L-dopa into the brain can be competitively inhibited by neutral amino acids such as leucine and phenylalanine in the diet since the drug enters the brain via the neutral amino acid transporter system[8]. This only affects the response to but not the plasma concentration of L-dopa, thereby producing an apparent alteration in pharmacodynamics. Studies in experimental animals and the use of inhibitors of transporters may be required to elucidate the mechanism of such interactions.

Our studies of the pharmacodynamics of drug action in disease states, using animal models, were initiated with a survey of the clinical literature for evidence suggestive or indicative of disease effects. Our emphasis was on drugs acting on the central nervous system although our earlier clinical studies had focused on directly and indirectly acting anticoagulants, *i.e.*, heparin[9] and dicumarol[1]. To facilitate a relatively wide exploration, rodents were used and a number of different models of disease were activated. Whenever possible, experimental disease states were produced by more than one method (*e.g.*, renal failure was produced by ligation of ureters or by administration of uranyl nitrate) to minimize the likelihood of method-specific artifacts. The drugs were administered in their optically pure form; racemic mixtures were not used except to confirm clinical reports (*i.e.*, thiopental). The experimental methodology was relatively simple, inexpensive, and designed to avoid quantitative errors in the estimation of effective drug concentrations due to a slow distribution of a drug to its site of action. In essence, this involved intravenous infusion of a drug, at different rates, until the onset of a predefined pharmacologic effect and determination of drug concentrations in different fluids or tissues at the pharmacologic endpoint[10]. Occasionally, offset

of effect was used as an additional endpoint to determine the possible role of pharmacologically active known or possibly unknown active metabolites[11].

The initial studies were designed to replicate, as much as possible, certain previously published clinical observations. The results were highly encouraging inasmuch as they demonstrated an increased sensitivity of the central nervous system (CNS) to the depressant effects of barbiturates in renal failure and in hypovolemia, and increased sensitivity to the convulsant effects of theophylline in renal failure, all being consistent with preceding clinical reports. Subsequent studies were performed on various disease models including liver disease, diabetes, hypertension and thyroid diseases. What should be the role of these preclinical studies in the safe and effective use of drugs in the clinical setting? These investigations can provide signals of disease-associated alterations in the pharmacodynamics (and pharmacokinetics, if appropriately designed and interpreted) of drugs and thereby alert physicians and clinical pharmacists to the possibility of similar disease effects in humans. An awareness of this possibility may lead to earlier recognition of quantitative changes of drug action in certain diseases, perhaps as early as in phase II or III drug development studies. At the very least, a cautionary statement in the product package insert based on the observations in animal models (and so stated) can alert medical practitioners and may eventually provide epidemiological confirmation or evidence to the contrary. There are also more fundamental benefits that can derive from the preclinical studies. For example, it was found that accumulation of an endogenous, low molecular weight substance in renal failure is associated with the increased CNS sensitivity to barbiturates in that pathologic condition[12].

I wish to express my thanks and appreciation to my collaborators, who, as postdoctoral fellows, graduate students and technicians, skillfully and energetically performed the studies described in this collection of reprints of published articles. They deserve the major credit for what has been accomplished. I thank the tax payers of the United States of America who provided the financial resources for our research via grants from the U.S. National Institutes of Health. Finally, my special thanks and appreciation to Professor Sergio Erill and the Esteve Foundation for publishing this collection and distributing the book gratis to various biomedical institutions, teachers and investigators. I hope that readers will be stimulated and encouraged to pursue further research on the kinetics of drug action in disease states.

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