

# Pharmacokinetic-Pharmacodynamic Modeling of Antihypertensive Drugs: Its Application to Clinical Practice

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## ABSTRACT

Knowledge of pharmacokinetic-pharmacodynamic (PK/PD) properties of antihypertensive drugs may optimize drug therapy of hypertension. PK/PD modeling in clinical research could contribute in drug development and clinical practice in several aspects, including an evaluation of the efficacy and safety of antihypertensive agents, enhancement of information during the development process, identification of factors that contribute to drug response variability, by allowing a rapid identification of poor or non-responders and by helping to determine optimal antihypertensive drug and dose requirements in each hypertensive patient. There are some limitations in PK/PD modeling of antihypertensive drugs in the clinical setting, including application of inadequate pharmacodynamic models and the inability to study large doses of antihypertensive drugs in order to determine the complete pharmacodynamic range of their antihypertensive effect.

The aim of the present review is to describe the current knowledge of PK/PD modeling of antihypertensive drugs in basic and clinical research and its future applications.

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Abbreviations >			
EC <sub>50</sub>	Half effective concentration	ABPM	Ambulatory blood pressure monitoring
ED <sub>50</sub>	Half effective dose	PD	Pharmacodynamics
Emax	Maximum effect	PK	Pharmacokinetics
ACEIs	Angiotensin -converting enzyme inhibitors	S <sub>0</sub>	Basal sensitivity

## BACKGROUND

Current antihypertensive therapy has two disadvantages which limit the efficacy of the therapeutic proposal to reduce cardiovascular mortality. Firstly, the results of antihypertensive therapy are suboptimal, and only one third of hypertensive patients receiving monotherapy are able to bring blood pressure under control. (1, 2) Observational clinical trials have demonstrated that blood pressure control may be achieved with the association of antihypertensive drugs. (1)

Failure in optimal dosage of antihypertensive drugs is another disadvantage. (3) Thiazide diuretics and beta blockers are currently indicated in doses that are significantly lower than those initially recommended; in this way, in past times patients with hypertension had been unnecessarily exposed to higher doses of these agents and were at greater risk of toxicity. (3) In addition, angiotensin—converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists are currently indicated at higher doses than those initially approved due to tissue-protective properties. (3)

Assessment of pharmacokinetic-pharmacodynamic (PK/PD) properties of antihypertensive drugs may optimize drug therapy of hypertension using PK/PD modeling. The integration of pharmacokinetics and pharmacodynamics might help to individualize the choice of antihypertensive drugs, dose requirements and time interval between doses in each hypertensive patient. (4-7)

The aim of the present review is to describe the current knowledge of PK/PD modeling of antihypertensive drugs and its contribution to optimize antihypertensive therapy.

## PRINCIPLES OF PK/PD MODELING

Pharmacokinetic/pharmacodynamic models build bridges between drug pharmacokinetics (PK) – the study of the time course of the drug concentration in the body - and the intensity of the pharmacological response, quantified by pharmacodynamics (PD). (4) This link is established through mathematical models that estimate parameters such as the concentra-

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tion of the drug required to produce 50% of the drug's maximum effect ( $EC_{50}$ ) and maximum effect ( $E_{max}$ ). PK/PD modeling provides information about the onset, magnitude, and duration of the therapeutic effect. (8) Figure 1 illustrates the principle of PK/PD modeling. It should be emphasized that although half effective dose ( $ED_{50}$ ) is considered an indicator of potency of antihypertensive agents,  $ED_{50}$  is a hybrid parameter that depends not only on the affinity of the drug with its target molecules but also of its pharmacokinetic characteristics. Therefore, it is essential to estimate "pure" pharmacodynamic parameters, such as  $CE_{50}$ , in order to guarantee an adequate dosage of antihypertensive drugs.

PK/PD modeling requires the simultaneous measurement of tissue drug levels and its corresponding pharmacological effects at multiple time points. (5) PK/PD modeling should fulfill certain validation parameters, such as continuity, sensitivity, objectivity and repeatability. (6)

The number of measurements of tissue drug concentrations and their corresponding effects must be as large as possible in order to obtain the greatest precision in estimating PK/PD relationship. (5) However, multiple time point sampling is not always possible in the clinical setting as it would require hospitalizing all hypertensive patients. Population PPK and PK/PD models have been introduced to overcome this limitation as they only require 2 or 3 sample time points. (9)

It is also important to estimate the delay between drug response and tissue levels. (5) Plotting drug effects as a function of drug concentrations and connecting data in a chronological order allows the determination of a possible disconnection between plasma levels and blood pressure lowering effect. A hysteresis loop appears in the plotting when the magnitude of an effect corresponds to more than one drug concentration. A counter clockwise hysteresis loop may be explained by an imbalance between the site of action and the plasmatic compartment, (10) by the appearance of active metabolites (11) or by indirect mechanisms of drug action. (12) On the other hand, a clockwise hysteresis loop suggests tolerance development to drug effects. (13)

In the absence of temporal disconnection between tissue concentrations and pharmacological response, plasma levels may be directly related with the pharmacological effect. (9) Table 1 describes PD models used for PK/PD modeling.

The most widely accepted PD model for the assessment of PK/PD relationship is the maximum effect ( $E_{max}$ ) which estimates drug potency and efficacy (Table 1). Nevertheless, PK/PD parameters using the  $E_{max}$  model needs the determination of the complete pharmacodynamic range after the administration of a single dose of the drug; thus a high dose is required to reach a magnitude of the drug effect close to its maximum response. (5) When the  $E_{max}$

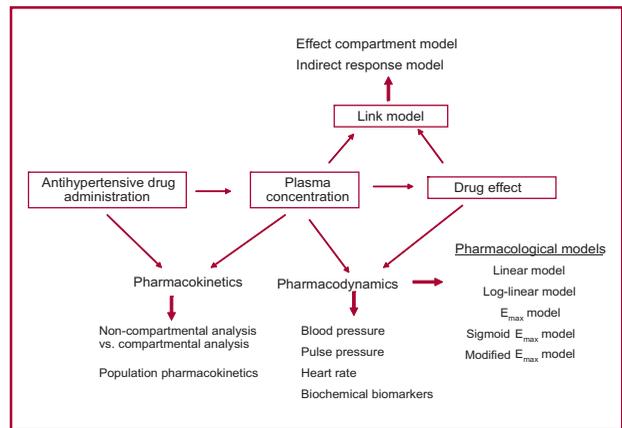


Fig. 1. Principles of PK/PD modeling of antihypertensive drugs

model is used to estimate a curve without a clear maximum,  $E_{max}$  and  $EC_{50}$  estimations are extremely variable. (14) Schoemaker et al. designed a modified pharmacodynamic model by replacing the parameter  $E_{max}/EC_{50}$  with  $S_0$  in the  $E_{max}$  equation.  $S_0$  is a more stable parameter defined as the initial sensitivity to the drug at low concentrations.

In presence of delay, plasma concentrations may not be directly related to the pharmacological effect, and more complex PK/PD are needed (effect compartment model and indirect-response model). (9)

### Justification of PK/PD Modeling of Antihypertensive Drugs

Most antihypertensive agents have a reversible mechanism of action and the magnitude of the effect is strongly related to tissue levels. (15) Some antihypertensive drugs, such as ACEIs, are capable of generating active metabolites and plasma levels of these metabolites should be related to pharmacological response. (15)

PK/PD modeling of antihypertensive effect is justified considering that blood pressure is an excellent biological marker of long-term clinical efficacy of antihypertensive drugs. (16, 17) A great number of comparative randomized trials have demonstrated small differences in the incidence of cardiovascular morbidity and mortality among antihypertensive drugs for similar reductions in blood pressure levels. (8)

Blood pressure fulfills the requirements of a pharmacological effect for PK/PD; continuity, sensitivity, objectivity and repeatability. (16)

### Methodological Aspects

It is extremely important to determine which PK/PD model is going to be applied for data analysis to prevent an erroneous interpretation. (18) Harder et al. (9) found that the slope for the hypotensive effect of

**Table 1.** Common pharmacodynamic models used for PK/PD modeling of antihypertensive drugs

Pharmacodynamic model	Equation	Comment
Linear model	$E = S * C + E_0$	This model erroneously assumes that the effect can increase with concentrations without limits
Log-linear model	$E = S * \log C + E_0$	Impossible to predict the value of E when C = 0 Impossible to predict the maximum effect
$E_{\max}$ model	$E = E_0 + \frac{E_{\max} * C^\gamma}{CE_{50}^\gamma + C^\gamma}$	Broadly used to characterize pharmacological effects
Sigmoid $E_{\max}$ model	$E = E_0 + \frac{E_{\max} * C}{CE_{50} + C}$	More convenient to fit steep pharmacological responses
Modified $E_{\max}$ model	$E = E_0 + \frac{S_0 * E_{\max} * C}{E_{\max} + S_0 * C}$	Can be applied to pharmacological responses without reaching the maximal effect

verapamil after the administration of a single dose was significantly greater than the slope estimated after multiple dosing. Although they concluded that tolerance to verapamil was due to chronic exposure to the drug, probably higher degree of the concentration-response curve of verapamil may be achieved due to higher drug concentration at steady state. (20) We have found a dose-dependent reduction in verapamil slope estimation after applying the linear model in rats with aortic coarctation. (21) As pharmacological response increases slower at the higher part of the concentration-response curve, a lower slope is obtained after the administration of a higher dose compared to a lower one. (21) In addition, we have demonstrated that the  $E_{\max}$  equation does not allow an exact estimation of PK/PD parameters of the hypotensive effect of diltiazem, considering that estimations of  $CE_{50}$  were dose-dependent. (22) Conversely, the modified  $E_{\max}$  model designed by Schoemaker et al. allows both a precise and accurate estimation of the sensitivity to hypotensive effect of diltiazem in conditions when maximum pharmacological response can not be attained. (14, 22)

A time delay between the hypotensive effect and plasma concentration should be considered. Traditionally it was thought that there was no relationship between beta blockers and changes in blood pressure. Nevertheless, we have found a correlation between metoprolol levels and its antihypertensive effect in different models of experimental hypertension applying a PK/PD effect compartment model. (23-26). The rational use of this model is based on the mechanism of antihypertensive effect of beta blockers that includes an action on the central nervous system in case of lipid-soluble beta blockers. (27)

Most PK/PD studies of ACEIs have applied a PK/PD model with an effect compartment to account for time delay in the onset of the cardiovascular response.

(28-30) This might be explained by inhibition of angiotensin-converting enzyme and reduction in the synthesis of angiotensin II.

In PK/PD modeling of antihypertensive drugs it is important to consider the existence of a placebo response and the circadian variation of blood pressure. Therefore, in the study of PK/PD properties of antihypertensive drugs in normotensive volunteers and hypertensive patients it is necessary to estimate the placebo response and include it in the model for an exact estimation of PK/PD parameters. (31, 32)

Control of blood pressure may be performed with conventional cuff blood pressure measurements and 24-hour ambulatory blood pressure monitoring (ABPM). Trocóniz et al. (32) found that estimation of population PK/PD parameters for the antihypertensive effect of moxonidine did not differ from manual blood pressure measurements and 24-hour ABPM measurements. Nevertheless, ABPM offers a detailed description of the individual pharmacodynamic profiles of moxonidine and individualization of the therapy. (32)

Pharmacodynamics of antihypertensive drugs acting on the renin-angiotensin system could also be monitored by determination of renin activity. (33, 34) Plasma renin concentration may be a suitable biomarker of cardiovascular effects of drugs acting on the mentioned system. (33)

Another aspect to consider is the selection of the tissue samples to monitor antihypertensive drug concentrations. (7) It should be noted that blood pressure is regulated by an interaction of tissues and organs. (15) It has been proposed that antihypertensive effect of beta blockers is a consequence of beta-adrenergic blockade in myocardium, kidneys and central nervous system. (15) Then blood sampling would be an adequate means to control antihypertensive drugs concentrations and to make a correlation with their effects.

Table 2 summarizes the recommendations for experimental design and data analysis for PK/PD modeling.

## APPLICATIONS IN CLINICAL PRACTICE

### Variability of Antihypertensive Response

The rational selection of the safest antihypertensive agent is based on the information obtained from the physical examination (age, sex, race, smoking habits, obesity and lipid levels); however, factors that determine the response to the different antihypertensive drugs are not clearly understood, as there is no reliable method for identifying which patients will respond to which drugs. (35)

It is important to consider that the magnitude of the antihypertensive response is determined, in part, by the individual sensitivity to the pharmacological effect and by the amount of drug which reaches the target site. Nevertheless, most clinical studies have not assessed plasma concentrations of antihypertensive drugs; therefore they do not provide convincing information related to the sources of variability of cardiovascular response. For example, the antihypertensive response to verapamil is greater in the elderly (36) but it is not clear if this improved efficacy is the result of an increase in the sensitivity to the drug or is the consequence of greater plasma levels due to a reduced clearance of verapamil.

Most studies of antihypertensive drugs have estimated ED<sub>50</sub> as a way to assess drug potency. ED<sub>50</sub> is a hybrid pharmacokinetic and pharmacodynamic parameter because it combines EC<sub>50</sub> with parameters of drug clearance and bioavailability. (5) For this reason, this estimation fails to establish the sources of variability of the response to antihypertensive drugs. (5)

PK/PD modeling could be a powerful tool for the study of determinants of the antihypertensive responses to different drugs. For instance, PK/PD studies of alpha-adrenergic blockers (prazosin and doxazosin) demonstrated that long-term responses to therapy are independent of basal blood pressure values and of the pharmacological response to the first dose. (37, 38) Donnelly et al. (30) did not find any relationship between sensitivity to enalapril (E<sub>max</sub> or EC<sub>50</sub>), patient's age or renin activity, but they observed a positive correlation between E<sub>max</sub> and blood pressure values previous to treatment. Murray et al. (39) demonstrated that the first-dose blood pressure response to ACE inhibition cannot be accurately predicted from baseline physiopathological variables in patients with congestive heart failure.

Interestingly, pharmacogenetics research has identified variations in particular genes which have effect on the metabolism of antihypertensive drugs and might have influence on antihypertensive pharmacodynamics. (40, 41) The use of PK/PD modeling for the analysis of the impact of genetic variation on an-

**Table 2.** Recommendations for PK/PD modeling of antihypertensive drugs

#### Experimental design

- Frequent plasma sampling and individual pharmacokinetics; could be used in phase I or II PK/PD studies
- Sparse blood sampling with population pharmacokinetics is recommended in PK/PD studies in the clinical setting.
- Blood pressure should be monitored by ABPM because it provides plenty of data.
- Blood pressure response to placebo should be estimated before the administration of drugs.
- PK/PD study should assess different antihypertensive drug doses.

#### Data Analysis

- Antihypertensive plasma concentrations should be analyzed by compartment models.
- Blood pressure lowering effect needs to be corrected by placebo response.
- Determine the existence of any temporal disconnection between antihypertensive drug plasma concentration and the corresponding pharmacological response.
- If a temporal disconnection exists, a PK/PD link model should be applied for data analysis.
- It is important to select the adequate PD model to estimate PK/PD parameters. If possible, compare the estimation of PK/PD parameters by different PD models. Selection of PD model should not only be based on goodness of fit but also on accuracy and precision of the PK/PD parameter.
- Compare PK/PD parameter estimation obtained from different dose concentrations to validate the PD model. It is important to consider that, in most cases, PK/PD parameters are dose-independent.

tihypertensive response might improve our understanding of determinants of antihypertensive drug response so as to individualize drug selection.

### Early Detection of Responders

Currently there are no clear determinants of the pharmacological response to antihypertensive drugs; therefore the selection of the initial therapy is empirical. An early detection of poor responders to individual antihypertensive drugs might accelerate the choice of the appropriate regime.

Several PK/PD studies have demonstrated that sensitivity to the first dose of antihypertensive drugs correlates with the response after one to six weeks of treatment, suggesting that the acute effect would predict the response along the chronic therapy.

PK/PD modeling might be useful for the early identification of poor responders or non-responders and for determining individual dose requirements for an optimum long-term blood pressure control. (35)

One disadvantage for PK/PD modeling is the need of plasma sampling for antihypertensive drug concentrations monitoring. Population PK/PD modeling al-

lows the estimation of PK/PD properties of antihypertensive drugs with sparse blood sampling, considering that only two to three time points are needed when using population pharmacokinetics. (42, 43)

### Optimization of Antihypertensive Drug Regimen

Optimal blood pressure control requires pharmacological treatments that reduce blood pressure levels during 24 hours. Although it must be considered that all antihypertensive drugs licensed for once daily administration have comparable duration of action, it is well known that these agents differ in this issue. Estimation of trough-to-peak ratio is an excellent index of the duration of action of an antihypertensive drug. (44) Antihypertensive agents which show high trough-to-peak ratio exert a short blood pressure lowering effect, requiring high dosage to reduce adequately blood pressure along 24 hours. (44) However, this therapeutic strategy is associated with a profound fall in blood pressure at the time of peak drug effect, increasing the risk of hypotension. (44)

A satisfactory trough-to-peak ratio (60%) indicates that the duration of the action of antihypertensive drugs is appropriate for the chosen dose interval. (44) Thus, estimation of PK/PD parameters of antihypertensive drugs and further simulation of the response profiles for a range of alternative dosage regimens allows the identification of the optimal dose and dose interval of an antihypertensive agent in each hypertensive patient. Meredith et al, (45) studied PK/PD properties of a single dose of enalapril using the estimated parameters to simulate blood pressure profiles during chronic treatment with several alternative dosage regimens. They found great interindividual differences in dose requirements and dose interval in order to achieve an optimal trough-to-peak ratio and full 24-hour blood pressure control. (45)

### Optimal Dosage Schedule of Antihypertensive Drugs

PK/PD modeling allows the study of the delay in the onset of the pharmacological effect. It is well known that blood pressure varies according to the time of the day, rising rapidly in the morning upon awakening. (46) In dipper hypertensive patients, blood pressure decreases 10%-20% during the night. (46) In order to achieve an adequate control of blood pressure it is necessary that the maximum antihypertensive response occurs during the rise of blood pressure and a minimum effect during trough blood pressure values so as to reduce the risk of excessive hypotension. Selection of the optimal dosage schedule of antihypertensive drugs depends on drug pharmacokinetics. This may be a rational strategy for antihypertensive agents that do not show a delay in pharmacological response, such as calcium antagonists. On the other hand, monitoring of plasma concentrations of antihypertensive drugs with slow pharmacological response

and irreversible or pseudo-irreversible mechanism of action could fail to estimate accurately the optimal time of dosage. PK/PD models allow the quantification of the time delay in the onset of the pharmacological action of antihypertensive drugs. Several studies have found dissociation between plasma levels of antihypertensive drugs, including alpha blockers, beta blockers, ACEIs, angiotensin II receptor antagonists and central antihypertensive drugs, and their pharmacological response. Therefore, for these antihypertensive drugs, the delay in the onset of action determined by PK/PD modeling must be added to the delay in achieving maximum plasma concentration after an oral dose in order to estimate the optimal dosage schedule.

### Assessment of Clinical Relevance of Drug Interactions

Drug interactions may greatly affect antihypertensive therapy by reducing or enhancing blood pressure lowering effect of these drugs. (47) Antihypertensive therapy generally needs the administration of a combination of blood pressure lowering drugs, and the study of the association of these drugs is important. Different mechanisms participate in drug interaction, including alterations in drug disposition, drug clearance, and pharmacodynamic changes. (46) PK/PD modeling studies might elucidate the relevance of different interactions in antihypertensive therapy.

Schaefer et al. (48) assessed a drug-food interaction with PK/PD modeling for a controlled-release nisoldipine dosage form. The relationship between nisoldipine plasma concentration and its cardiovascular effects was studied with the Emax model. Food increased maximum blood pressure lowering response by about 10% by increasing plasma concentrations of nisoldipine. (48)

PK/PD modeling is a useful tool to assess the combination of antihypertensive drugs. Huang et al. (49) studied the interaction between irbesartan and hydrochlorothiazide in renal hypertensive dogs using the PK/PD modeling and demonstrated that irbesartan increases plasma concentrations of hydrochlorothiazide at steady state. (49) In addition, combination of hydrochlorothiazide with irbesartan increased the sensitivity and efficacy of the blood pressure lowering effect of the AT1 estimated by CE50 and Emax. (49)

Meredith and Elliot (44) have evaluated the role of PK/PD modeling as a tool to assess the clinical efficacy of a combination of prazosin and verapamil. Supine diastolic blood pressure responsiveness was significantly higher at  $3.3 \pm 0.5$  mm Hg per ng/ml when prazosin was combined with verapamil ( $p < 0.01$ ) compared to  $2.4 \pm 0.5$  mm Hg per ng/ml for standard doses of prazosin alone, suggesting the existence of both pharmacokinetic and pharmacodynamic components in this interaction.

Type of studies	Applications
<b>Preclinical studies</b>	<ul style="list-style-type: none"> <li>- Precise definition of dose-concentration-pharmacological effects ratio and dose-concentration-toxicity ratio.</li> <li>- Determination of the appropriate dosage regime for studies in phase I.</li> <li>- Identification of biological markers and animal models for efficacy and toxicity.</li> <li>- Explore any dissociation between plasma concentration and the onset and duration of the pharmacological effect.</li> <li>- Provide information on drug effects that would be difficult to obtain from human beings.</li> </ul>
<b>Clinical research</b>	<ul style="list-style-type: none"> <li>- Study of determinants of variability in antihypertensive response</li> <li>- Assessment of the efficacy of antihypertensive drugs combination.</li> <li>- Exploration of the relationship between dose-concentration-effect of investigational antihypertensive drugs in patients.</li> <li>- Study of tolerance development to antihypertensive agents.</li> </ul>
<b>Clinical practice</b>	<ul style="list-style-type: none"> <li>- Early detection of poor responders or non-responders.</li> <li>- Optimization of antihypertensive drug regimes in terms of doses, sampling interval and time of dosing.</li> <li>- Assessment of clinical impact of drug interactions</li> </ul>

**Table 3.** Applications of PK/PD modeling of antihypertensive studies

## CONCLUSIONS

Several studies have found that blood pressure response to antihypertensive drugs is clearly related to tissue levels of these drugs and, therefore, PK/PD modeling allows a better understanding of pharmacokinetic/pharmacodynamic characteristics of these agents.

Experience with PK/PD modeling has demonstrated its role to improve the clinical use of antihypertensive drugs. This methodology not only contributes to optimize drug dosage and patient selection in clinical practice, but also enhances the information on new antihypertensive drugs during their development process.

Although PK/PD modeling is frequently used in different phases of drug development, (4) the role of PK/PD modeling in clinical practice remains unknown.

PK/PD modeling of antihypertensive drugs has a great clinical impact, as it allows a rapid assessment of long-term response of antihypertensive therapy and selection of the optimal dosage schedule in each patient. Nevertheless, there are some limitations in PK/PD modeling of antihypertensive drugs in the clinical setting: 1) ignorance of PK/PD modeling concepts, 2) requirements of special computer-assisted programs, (9) and 3) simultaneous plasma concentration monitoring of antihypertensive drugs with measurement of blood pressure lowering effect. Frequent blood sampling is a disadvantage of PK/PD studies. Thus, population pharmacokinetics is more frequently used to estimate PK/PD characteristics. (42, 43) Population PK/PD modeling is expected to increase its applica-

bility to individualize antihypertensive drug therapy in the clinical setting.

In conclusion, PK/PD modeling might significantly improve pharmacological treatment of hypertension by establishing optimal drug and dosage regime for each hypertensive patient (Table 3). Even more, PK/PD modeling also contributes to study the sources of variability of antihypertensive response to those therapeutic agents.

The conceptual background presented in this review guarantees the need of pharmacokinetic-pharmacodynamic analysis for all antihypertensive drugs used in clinical practice. Nevertheless, it may be difficult to put this methodology into practice as it is technically complex and almost unavailable for attending physicians. Regulatory authorities should demand the pharmaceutical industry to perform PK/PD studies during drug development process and to publish the results in the drug package insert in order to enable physicians to improve the indication of antihypertensive drugs to their patients.

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