EXPERT OPINION

Models for evaluating the pharmacokinetics and pharmacodynamics for β-blockers

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Introduction: β-blocker therapy plays an important role in the treatment of various diseases, including hypertension, myocardial infarction and heart failure. Although all β-blockers shared their ability to competitively block β_1-adrenoceptor, this therapeutic class showed great heterogeneity in their pharmacokinetic (PK) and pharmacodynamic (PD) properties.

Areas covered: The present review describes the models used for PK and PK/PD evaluation of β-blockers and their applicability in preclinical and clinical studies. PK behavior of different β-blockers has been studied by means of individual compartmental and population PKs, allowing the estimation of relevant PK parameters and factors involved in intersubject variability. Different PK/PD models have been developed for the *in vivo* estimation of PD parameters of different cardiovascular effects of β-blockers.

Expert opinion: PK models and PK/PD modeling have clearly contributed to characterization of the PK and PD properties of β-blockers. Differences in cardiovascular actions between classical β-blockers and vasodilatory β-blockers need to be further studied in order to confirm the clinical benefits of the new-generation of β-blockers. PK/PD modeling may contribute to clarify the importance of heterogeneity of PK and PD properties of β-blockers potentially improving the selection of the adequate agent and dose regimen in the treatment of cardiovascular diseases.

Keywords: blood pressure, heart rate, pharmacokinetic–pharmacodynamic modeling, population pharmacokinetics, β blockers

Expert Opin. Drug Metab. Toxicol. (2014) ***10****(4):525-541*

1. Introduction

The introduction of β-blockers into clinical practice in the early 1960s has represented a major advance in cardiovascular pharmacotherapy [1]. Use of these drugs has clarified the role of the sympathetic nervous system in the etiology of diverse cardiovascular diseases and has clearly contributed to increase survival of patients affected by cardiac conditions [1]. Nowadays, β-blocker therapy plays an important role in the treatment of various diseases such as hypertension, stable angina, myocardial infarction, and more recently, systolic heart failure. Recent European guidelines for the management of hypertension continue to consider β-blockers as first-line antihypertensive agents for the initiation of pharmacological treatment. β-blocker therapy is as effective as other first-line antihypertensive agents in preventing coronary outcomes and is highly effective in preventing cardiovascular events in patients with a recent myocardial infarction and those with heart failure [2]. As β-blockers

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Article highlights.

- Although all β-blockers shared their ability to competitively block the β_1-adrenoceptor, this therapeutic class shows great heterogeneity in their pharmacokinetic (PK) and pharmacodynamic (PD) properties.
- Population PKs have been used for the assessment of clinical variability in PK properties of different β-blockers.
- Mechanism-based PK/PD models have been developed with the effort to improve extrapolation and prediction properties of pharmacological actions of β-blockers.
- PK/PD modeling has been used for the prediction of PD properties of β-blockers in patients with hypertension, mild-to-severe heart failure and in subjects after myocardial infarction with left ventricular dysfunction.
- The design of clinical studies focusing on the comparison of PK/PD models between cardioselective β-blockers and vasodilatory β-blockers may contribute to further clarify the benefits of additional pharmacological properties in the treatment of cardiovascular diseases.

This box summarizes key points contained in the article.

competitively inhibit the cardiotoxic effects of circulating catecholamines, they are able to reduce myocardial oxygen consumption by reducing heart rate, blood pressure and contractility [3]. In accordance, treatment with β-blockers was associated with a relative risk reduction of 13% of progression to acute myocardial infarction [4]. Treatment guidelines also have considered that β-blockers are of fundamental importance in modifying the course of systolic heart failure and must at least be considered in all patients in the absence of contraindications [5]. This recommendation is based on the results of several clinical trials that have demonstrated that treatment with certain β-blockers reduced mortality of patients with systolic chronic heart failure by about 35% after 1 year of treatment [5].

Although all β-blockers shared their ability to competitively block the β_1-adrenoceptor, this therapeutic class shows great heterogeneity in its pharmacokinetic (PK) and pharmacodynamic (PD) properties (**Table 1**). In this context, β-blockers mainly differ in the extents of gastrointestinal absorption, degree of hepatic first-pass metabolism, lipid solubility, protein binding, brain penetration, concentration within the cardiac tissue, rate of hepatic biotransformation and renal clearance of drug and/or metabolites [6]. These agents also exhibit differences in their PD profile, including β_1 selectivity, partial agonism, membrane stabilizing effect, presence of α-receptor antagonism and, more recently, direct vasodilatory properties [6].

The great diversity of PK and PD properties of the available β-blockers highlights the importance of the extensive preclinical and clinical evaluation of the pharmacological properties of these agents in order to optimize the treatment of cardiovascular diseases. The aim of the present review is to discuss the representative models for evaluating the PKs and PDs of β-blockers.

2. PK models of β-blockers

A large number of models have been applied for the characterization of PK behavior of β-blockers. The models developed in preclinical and clinical studies can be classified as individual PK models and population PK methods. Individual PKs are based in blood sampling and measurement of plasma drug concentrations at multiple time points in each experimental subject [7]. Main PK parameters, including rate constant of elimination (Ke), clearance (CL) and volume of distribution (Vd) are estimated by the use of specific PK models included in specialized software, such as WinNonLin, ADAPT II and Topfit [7]. Population PK methods have the ability to estimate PK parameters of drugs using a low number of plasma samples and are therefore attractive approaches for the evaluation of PK properties in special populations, including the critically ill, neonates and children [7]. Population PKs are able to simultaneously estimate population and individual PK parameters, to provide an estimate of between-subject variability and to investigate the effects of covariate on PK behavior of drugs [7].

2.1 Individual PKs of β-blockers

Individual PKs have been extensively used for the study of PK models of β-blockers, particularly in preclinical studies and clinical studies, including a limited number of subjects. PK models developed for β-blockers include compartmental models and, more recently, physiologically based models. PK properties of β-blockers differ considerably due to differences in their lipophilicity. Consequently, different compartmental models have been described for the study of individual PK of β-blockers. One-compartment or two-compartment PK models have been frequently used for the description of PK of hydrophilic β-blockers, including atenolol and esmolol. In the case of β-blockers with higher lipophilicity, including carvedilol, metoprolol and propranolol, two or three compartment PK models better fit to the plasma concentration profile of these drugs.

2.2 Compartment PK models

The use of compartmental analysis of individual PK of β-blockers has greatly contributed to the evaluation of the stereoselectivity of these drugs and the factors affecting PK behavior [8]. For instance, preclinical and clinical studies have demonstrated that the enantiomers of almost all β-blockers exhibit different PK properties, including Vd and CL [9,10]. The concentration time profile of carvedilol was studied in normotensive and hypertensive rats by means of traditional blood sampling and stereoselective quantification of both enantiomers [11-13]. Temporal course of S-carvedilol and R-carvedilol showed a biexponential decay of plasma levels compatible with a two-compartment PK model [11-13]. Individual PK analysis has demonstrated significant differences in main PK parameters, considering that both the Vd and CL of S-

Table 1. Main pharmacokinetic and pharmacodynamic properties of β-blockers.

	β_1-selectivity	ISA	Vasodilator effect	Lipophilicity	Elimination	Biopharmaceutical system class classification
Acebutolol	+	+	0	Moderate	H	3
Atenolol	++	0	0	Low	R	3
Betaxolol	++	0	0	Moderate	H/R	n/a
Bisoprolol	+++	0	0	Moderate	R/H	1
Bucindolol	0	+	+ (α_1-blockade)	Moderate	H	n/a
Carteolol	0	+	0	Low	H/R	n/a
Carvedilol	0	0	++ (α_1-blockade)	Moderate	H	2
Celiprolol	+	+	+ (β_2 Agonism)	Moderate	R	n/a
Esmolol	++	0	0	Low	R	n/a
Labetalol	0	+	++ (α_1-blockade)	Low	H	1
Metoprolol	++	0	0	High	H	1
Nadolol	0	0	0	Low	R	3
Nebivolol	+++	0	++ (NO availability increases)	Moderate	H	2
Pindolol	0	++	0	High	R/H	1
Propranolol	0	0	0	High	H	1

+: Low; ++: Moderate; +++: High; 0: Absence of effect; ISA: Intrinsic symapthomimetic activity; H: Hepatic; n/a: Not available; NO: Nitric oxide; R: Renal.

carvedilol were greater compared with the R-enantiomer in normotensive and hypertensive animals [11-13]. In the same way, preclinical studies using a two-compartment PK model have demonstrated significant enantioselective PK properties evidenced by a greater CL of L-nebivolol with respect to D-nebivolol [14].

Individual PKs have greatly contributed to the knowledge of the impact of physiopathological factors involved in the PK profile of β-blockers and the selection of the appropriate dose regimen in special populations. Early studies using compartment models or simply PK analysis from plasma concentrations have demonstrated that pregnancy, hyper or hypothyroidism, renal or hepatic failure, and congestive heart failure can modify PK behavior of β-blockers leading to the need of dose adjustment. The presence of renal failure differently affects plasma levels and response of individual β-blockers. McAinsh *et al.* [15] have found that atenolol half-life increased from 6 h in subject with normal renal function to > 100 h in patients with progressive renal failure with a corresponding increase in AUC. Repeated dose studies have shown an association between pre-dose atenolol plasma levels and logarithm of creatinine CL [15]. Taking into account these findings, dose reduction of atenolol is recommended in patients with renal insufficiency [15]. In another individual PK study, the apparent first-order elimination rate constant and plasma CL of sotalol have been found to significantly correlate with glomerular filtration rate [16]. As drug elimination is greatly reduced in patients with renal failure, therapy with sotalol should start with a low dose and any increase in dosage should be made carefully [16].

The impact of kidney function on bisoprolol has also been established by traditional models by the study of single-dose PK in patients with varying degrees of renal impairment and in healthy controls [17]. The authors found a significant correlation between creatinine CL and elimination half-life, AUC and total CL of bisoprolol in patients with renal dysfunction [17]. Nevertheless, as bisoprolol showed a balanced CL, accumulation of the β-blockers in renal failure is unlikely and no adjustment of dose is necessary for subjects with mild to moderate dysfunction [17]. In another study, PK properties of carvedilol in hypertensive patients with renal insufficiency were compared with control subjects [18]. Following a single oral dose or multiple dosing AUC of carvedilol plasma levels was 40 – 50% in patients with renal disease compared with control hypertensive subjects [18]. As changes in PK behavior associated with reduced kidney function are modest in view of the large interindividual variability of carvedilol, no changes in dosing recommendations for carvedilol are warranted in patients with moderate/severe renal insufficiency [18].

Drozdzik *et al.* [19] compared the PK profile of atenolol in healthy volunteers and subjects with unilateral nephrectomy using a one-compartment open model. The authors have found a reduction of atenolol CL in patients with nephrectomy compared to the control groups, suggesting that this surgical procedure impairs elimination of atenolol and possibly other β-blockers predominantly eliminated via the kidney [19].

Traditional PK studies have also evaluated the impact of pregnancy on PK behavior of different β-blockers. Comparison of PK properties of propranolol in the antenatally and postnatally state showed that pregnancy did not affect elimination half-life, CL or Vd of the β-blockers [20]. Conversely, O'Hare *et al.* have found a trend for faster elimination of sotalol in pregnant women probably as a consequence of an increase in renal plasma flow and glomerular filtration rate [21]. The PK profile of labetalol was evaluated in eight

women with pregnancy-induced hypertension in the third trimester of pregnancy by means of individual PK models [22]. The terminal elimination half-life of labetalol in pregnant women was found to be several times shorter than that reported for normotensive volunteers or non-pregnant hypertensive patients [22].

PK properties of β-blockers have also been assessed in neonates and children by means of traditional PK models. Läer *et al.* have compared the PK profile of carvedilol over the first 12-h period after the initial dose in pediatric patients with congestive heart failure with healthy adult volunteers [23]. Elimination half-life of carvedilol was approximately 50% shorter in pediatric patients compared with healthy adult subjects, suggesting the need of further studies to define optimal dosing of carvedilol among the pediatric population [23]. In another report, the PK of atenolol has been studied after intravenous administration of a single dose in 10 children during cardiac electrophysiological studies [24]. The time course of plasma atenolol concentrations were best described by a two-compartment model and revealed that children have a slightly shorter terminal elimination half-life than that of adults [24]. Therefore, additional studies are required to define the optimal oral dose and dosing frequency of atenolol in children. The PK properties of sotalol were studied in neonates, infants and older children with tachyarrhythmia after a single oral dose [25]. After application of a standard compartment model-independent method, the authors found a linear relationship between main PK parameters of sotalol – total CL and Vd – and body surface area, creatinine CL, body weight and age [25]. In addition, the study reported a greater AUC of sotalol plasma levels in children with small body surface area suggesting that dose adjustment based on body surface area led to a larger exposure to the β-blocker [25].

Changes in thyroid function seem also to affect PK behavior of certain β-blockers requiring dose adjustment. Riddell *et al.* studied PK profile of propranolol after oral and intravenous administration in six hyperthyroid and six hypothyroid patients who received single oral and intravenous doses of propranolol when they had thyroid dysfunction and after conversion to euthyroid state [26]. Systemic CL of propranolol was significantly greater when the patients were hyperthyroid than when they had become euthyroid, suggesting that adequate β-adrenoceptor blockade in hyperthyroid patients may require higher propranolol dosage than expected [26].

2.3 Physiologically based PK models

Compartment models have predominantly been used to describe or fit plasma concentrations of β-blockers drug and metabolites in order to assure accurate estimation of main PK parameters [27]. Although pragmatic, compartmental models typically derived from the data are essentially descriptive [27]. A limitation of this approach is the lack of information governing the PK behavior of drugs in specific tissues that limit its usefulness to encounter variability in PKs among patients associated with aging, disease, concurrent therapies and other influences [27]. In order to solve this drawback, in the last years physiologically based PK (PBPK) modeling and simulation have been developed. This approach can be used to predict the PKs of drugs in human populations and to explore the effects of varying physiological parameters that result from aging, ethnicity or disease [28].

Compartmental PK models include a limited number of compartments related to kinetically distinguishable portion in the time course profile of plasma drug concentrations, which do not represent well-defined and physiologically distinct body organs [27]. In comparison, PBPK models consist of compartments corresponding to different tissues in the body, connected by the circulating blood system [29,30]. These compartments include the main tissues of the body, including adipose, bone, brain, gut, heart, kidney, liver, lung, muscle, skin and spleen, and are defined by a tissue volume and blood flow rate that are specific to the species of interest (**Figure 1**) [29]. PBPK modeling is already complex and data intensive, but can be used to predict the PKs of drugs in human populations and to explore the effects of varying physiological parameters that result from aging, ethnicity or disease [29].

Among few studies exploring the utility of PBPK modeling for prediction of β-blockers PK profile, Levitt has evaluated the effects of meal on propranolol oral absorption by means of PBPK modeling. Using the PKQuest software, the authors reported that meal increases portal blood flow by 50% and decreases liver metabolism of propranolol by 20% [31]. In addition, a significant delay in propranolol absorption has been detected in fasting subjects when compared with the fed state.

More recently, Gaohua *et al.* have developed a pregnancy PBPK model for the evaluation of the disposition of drugs metabolized by CYP1A2, CYP2D6 and CYP3A4 [32]. Using a perfusion-limited form of a 13-compartment full-PBPK model extended to the pregnancy state, the authors predicted a 30% decrease in the exposure of metoprolol in the pregnant women compared with the non-pregnant subjects [32].

2.4 Population PKs of β-blockers

In the last decades, the population PKs approach has greatly contributed in the knowledge of PK properties of β-blockers in the clinical setting (**Table 2**) [33]. Population PKs of β-blockers usually include sparse plasma sampling and the PK analysis of plasma concentrations by means of the nonlinear mixed effect modeling (NLME). The PK parameters of β-blockers in individual subjects are obtained from the population by Bayesian estimation, inference based on linearization or non-parametric Bayesian inference. Population PKs have been used for the assessment of clinical variability in PK properties of different β-blockers. Honda *et al.* [34] have evaluated the effect of CYP2D6 polymorphism on PK of R- and S-carvedilol in healthy volunteers. The authors estimated PK parameters of carvedilol in individual subjects by Bayesian method using nonlinear mixed effects model adjusting the data to a one-compartment model [34]. Population PK analysis

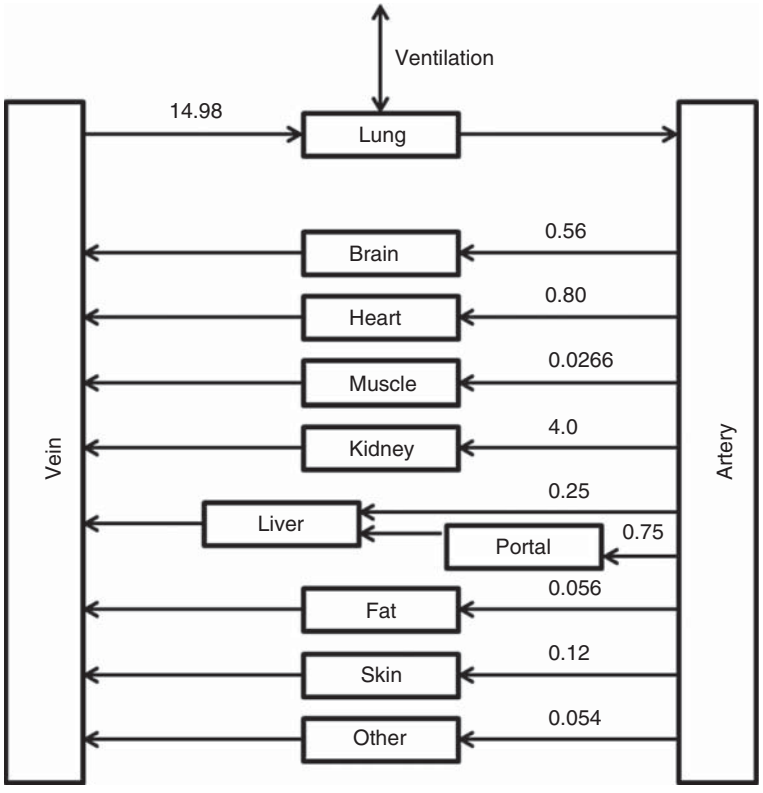

Figure 1. Physiologically based pharmacokinetic model for evaluation of β-blockers according to the model proposed by Levitt [31].

Numbers above arrows indicate tissue blood flow in l/min/kg.

have demonstrated that the presence of CYP2D6*10 allele is associated with a reduction in Vd and oral CL of carvedilol when compared with CYP2D6*1/*1 and *1/*2 carriers, suggesting that CYP2D6 polymorphism significantly influence systemic and pre-systemic metabolism of carvedilol [34]. In a second report, the authors have found that other polymorphisms at CYP2C9, CYP2C19, CYP3A5, UGT2B7 and MDR1 did not significantly affect the PKs of carvedilol in healthy subjects [35]. Factors influencing carvedilol PK have also been evaluated by means of a population PK approach in pediatric patients with congestive heart failure. Albers *et al.* [36] analyzed 408 carvedilol plasma samples of 41 pediatric patients assessing PK parameters by means of population PK adjusting to a two-compartment model with first-order absorption [36]. The authors reported that exposure to carvedilol measured by the area under the plasma concentration–time curve (AUC) as increased with age despite dose correction with respect to body weight [36]. In addition, Nikolic *et al.* [37] recently performed population PK analysis of controlled release (CR) carvedilol by NLME to estimate and identify different factors that could affect PK in patients with heart failure [37]. Total daily doses and drug plasma concentrations of carvedilol showed high interindividual variability and PK analysis demonstrated that total body weight, concomitant therapy with digoxin, and smoking are the main determinants of this variability [37].

Population PKs also represent an attractive tool to compare PK variability associated with the use of different formulations of β-blockers. In this context, a single population PK model has been developed to describe S-carvedilol PK from the immediate release (IR) and the CR dosage forms of the racemate [38]. In order to compare intersubject variability, PK parameters of S-carvedilol were estimated by means of a two-compartment model with first-order absorption and elimination. The main finding of the study was the detection of a lower intersubject variability in the rate of S-carvedilol oral absorption for the CR formulation with regards to the IR dosage form [38].

Taguchi *et al.* have evaluated population PK of metoprolol by means of nonlinear mixed effects model analysis adjusting to a one-compartment model in routinely treated Japanese patients [39]. A large interindividual PK variability of metoprolol has been found in middle age and elderly patients suggesting that the presence of CYP2D6*10 allele is responsible for decreased systemic CL and increased bioavailability [39,40].

The PK variability of bisoprolol was also established using the population PK approach in middle-aged and elderly patients [41]. After fitting the data to one compartment PK

Table 2. Main population PKs studies with β-blockers.

β-blocker	Population	PK model	Main findings	Ref.
Bisoprolol	Middle-aged and elderly patients	One-compartment model	Clearance of bisoprolol is associated to body weight and creatinine clearance	[41]
Carvedilol	Healthy volunteers	One-compartment model	CYP2D6*10 allele associated with reduction in clearance	[34]
Carvedilol	Healthy volunteers	One-compartment model	CYP2C9*3, CYP2C19*2, CYP2C19*3, CYP3A5*3, UGT2B7*2, and MDR1 C3435T did not significantly affect PK	[35]
Carvedilol	Pediatric patients with congestive heart failure	Two-compartment model with first-order absorption	Weight and age influence carvedilol PK	[36]
Carvedilol	Patients with congestive heart failure	One-compartment model	Carvedilol clearance depends on body weight, α(1)-acid glycoprotein and CYP2D6 genotype	[82]
Carvedilol	Patients with heart failure	Two-compartment model	Total body weight, concomitant therapy with digoxin and smoking are the main determinants of PK variability of carvedilol	[37]
Carvedilol	Healthy volunteers	Two-compartment model with first-order absorption and elimination	Lower intersubject variability in the rate of S-carvedilol oral absorption for the CR formulation with regards to the IR dosage form	[38]
Metoprolol	Middle-aged and elderly patients	One-compartment model	CYP2D6*10 allele associated with increase in bioavailability CYP2C19 genotype, gender and heart failure showed no significant effects on the PKs of metoprolol	[39,40]

PK: Pharmacokinetic.

model, a small intersubject variability has been described for bisoprolol, considering that CL of the drug showed a good correlation with body weight and creatinine CL and was not affected by CYP2D6 and CYP2C19 genotypes, gender or age [41].

3. PK/PD models of β-blockers

As β-blockers mainly act by reversible antagonism of β-adrenoceptors inducing diverse cardiovascular effects – blood pressure and heart rate reduction, attenuation of vascular sympathetic activity, among others – different PK/PD models have been described in preclinical and clinical studies. PK/PD relationships build a bridge between the time course of drug concentrations in the organism, as assessed by PK, and the intensity of the observed pharmacological response, as quantified by PD [42]. The link between PK and PD of a drug is established by the use of mathematical models, allowing the estimation of parameters such as effective concentration to yield half-maximal response (EC_{50}) and maximal efficacy (E_{max}). PK/PD modeling provides information about the onset, magnitude and duration of the therapeutic effect [43]. In this way, PK/PD modeling requires the simultaneous measurement of drug tissue levels and their corresponding pharmacological effects at multiple time points [44]. Measurements of the active compound should be performed with fully validated analytical methods [43]. Although ideally concentrations of the therapeutic agent should be measured at the target site, in most situations this is not possible and frequent plasma sampling is the only alternative [45]. In addition, an accurate measurement of the intensity of the pharmacological effect of the active compound is necessary for a PK/PD modeling design. A drug effect could be considered as any change in physiological parameters induced by the administration of a drug, compared to respective baseline values. Quantification of the effect should meet validation parameters such as continuity, sensitivity, objectivity and repeatability [45].

β-blockers met with the requirements for the study of PK/PD models. Due its chemical structure, tissue levels of β-blockers can be continuously monitored by means of highly sensitive analytical methods, especially liquid chromatography coupled to fluorescence detection [46-48]. Considering the stereoselectivity of the pharmacology of these drugs, several enantioselective chromatographic methods have been developed for the separation and quantification of R- and S-enantiomers of β-blocker [48].

On the other hand, the blood pressure lowering and chronotropic effects of β-blockers can be continuously monitored using different devices and also met with the required validation parameters. For instance, blood pressure and heart rate are excellent biomarker of the long-term clinical efficacy of antihypertensive drugs and shows continuity, sensitivity,

objectivity and repeatability [49]. Blood pressure has become a well-established surrogate end point, on the basis of natural history/epidemiologic data and numerous clinical trials of a variety of agents that correlate reductions in blood pressure with reductions in the risk of cardiovascular events [49]. Epidemiological studies have also demonstrated a relationship between increased heart rate and mortality [50]. In a long-term follow-up of the Framingham study, an increase in all-cause mortality by 14% at every increase in HR by 10 beat per minutes has been detected in the general population [50].

A large number of reasons justified the relevance of PK/PD modeling of cardiovascular response to β-blockers, including the enhancement of preclinical information during the development process, the identification of factors that contribute to drug response variability, the ability to identify poor or non-responders and the optimization of antihypertensive drug and dose requirements in each hypertensive patient [51].

3.1 Design of PK/PD models for β-blockers

PK/PD models developed for β-blockers differ in the PK data, PD end points and the mathematical models for the PK and PD relationship (**Figure 2**). Regarding PK data, total and unbound plasma levels of β-blockers have been commonly used in PK/PD studies. As only the S-enantiomer of β-blockers possesses β-blocking activity [10], models designed for the estimation of PK/PD parameters of chronotropic response to β-blockers usually include enantioselective methods and specific quantification of S-enantiomer plasma levels.

Taking into account that PK/PD modeling needs measurement of drug tissue levels at multiple time points, frequent plasma sampling could interfere with the PK and PD behavior of the β-blocker under evaluation due to fluid loss, especially in small laboratory animals [52]. In this way, the use of intra-arterial or intravenous microdialysis could be an interesting technique in order to overcome this methodological limitation [52,53]. A shunt intra-arterial microdialysis probe with one vascular inlet and two vascular outlets have been validated for the study of PK/PD models of β-adrenergic blockers and other antihypertensive drugs [53]. The inlet and one outlet are inserted into the left carotid artery and the remaining outlet is connected to a pressure transducer, allowing the simultaneous monitoring of cardiovascular parameters. Therefore, the shunt microdialysis probe serves for continuous arterial drug concentration monitoring and the corresponding antihypertensive response during PK/PD experiments [53,54].

Different pharmacological effects of β-blockers have been selected as PD end points in PK/PD studies. For β-blocker agents, the relationship is most prominent between plasma concentrations and the pharmacological effect of cardiac receptor antagonism and less clearly defined for changes in blood pressure [55]. As heart rate reduction induced by β-blockers mainly depends on competition with endogenous noradrenaline at myocardial β-adrenoceptors, the chronotropic response has been established as a suitable PD end point both in humans and in laboratory animals [56]. Although potency of β-blockers can be estimated by PK/PD modeling by the evaluation of drug effects on baseline heart rate, in some cases the bradycardic response induced by β-blocker administration is often small and difficult to distinguish from normal variations in heart rate, particularly in human being [56]. Therefore, in the clinical setting, PK/PD properties of chronotropic effect of β-blockers have been evaluated using isoprenaline-induced or exercise-induced tachycardia [56]. At this point, it is important to mention that the reduction of exercise tachycardia represent the gold standard for measurement of β_1-adrenergic blockade in human subjects, considering that heart rate response to isoprenaline is partly mediated by increase in heart rate in response to reduced diastolic blood pressure due to vasodilation.

Early reports suggested the absence of a relationship between plasma concentration of β-blockers and changes in blood pressure. For instance, a poor concentration–response relationship for the hypotensive effect of metoprolol has been found in some studies [57-59] but not in others [60,61]. The suggestion that there is no relationship between plasma levels of antihypertensive drugs and its effect on blood pressure reflects an inadequacy or failure in the approaches designed to detect such correlation. Several factors have hampered the possible identification of a correlation, including failure to study individual patients, inability to collect sufficient PD data, failure to identify and account for temporal delay in the onset of the pharmacological effect, the use of restricted concentration ranges and the use of dose rather than concentration [62,63]. In contrast to early findings, recent PK/PD models have been successfully developed for the estimation of *in vivo* PD parameters of the blood pressure lowering effect of different β-blockers in laboratory animals and clinical trials [51].

The availability of computational software for the spectral analysis of continuous blood pressure recording offers the opportunity for studying the relationship between third-generation β-blockers plasma levels and their effect on vascular sympathetic activity. Blood pressure shows rapid beat-to-beat oscillation due to the interplay of different cardiovascular control systems, including the baroreceptor reflex, the renin–angiotensin system (RAS), the vascular myogenic response and the release of nitric oxide (NO) from the endothelium [64]. The response times at which different neurohormonal systems operate vary considerably and, therefore, the analysis of beat-to-beat blood pressure variability by means of spectral analysis allows the estimation of the relative contribution of neurohumoral systems in blood pressure regulation. In this context, RAS peptides, catecholamines, endothelial-derived NO and myogenic vascular function affect blood pressure variability at very low frequency [64]. Conversely, low-frequency variability is affected by sympathetic modulation of vascular tone and endothelial-derived NO in rats [64]. Moreover, normalized LF (LF/HF ratio) has been validated as a marker of sympathetic vascular activity in preclinical and clinical studies [65]. In a previous study, a relationship between racemic carvedilol plasma

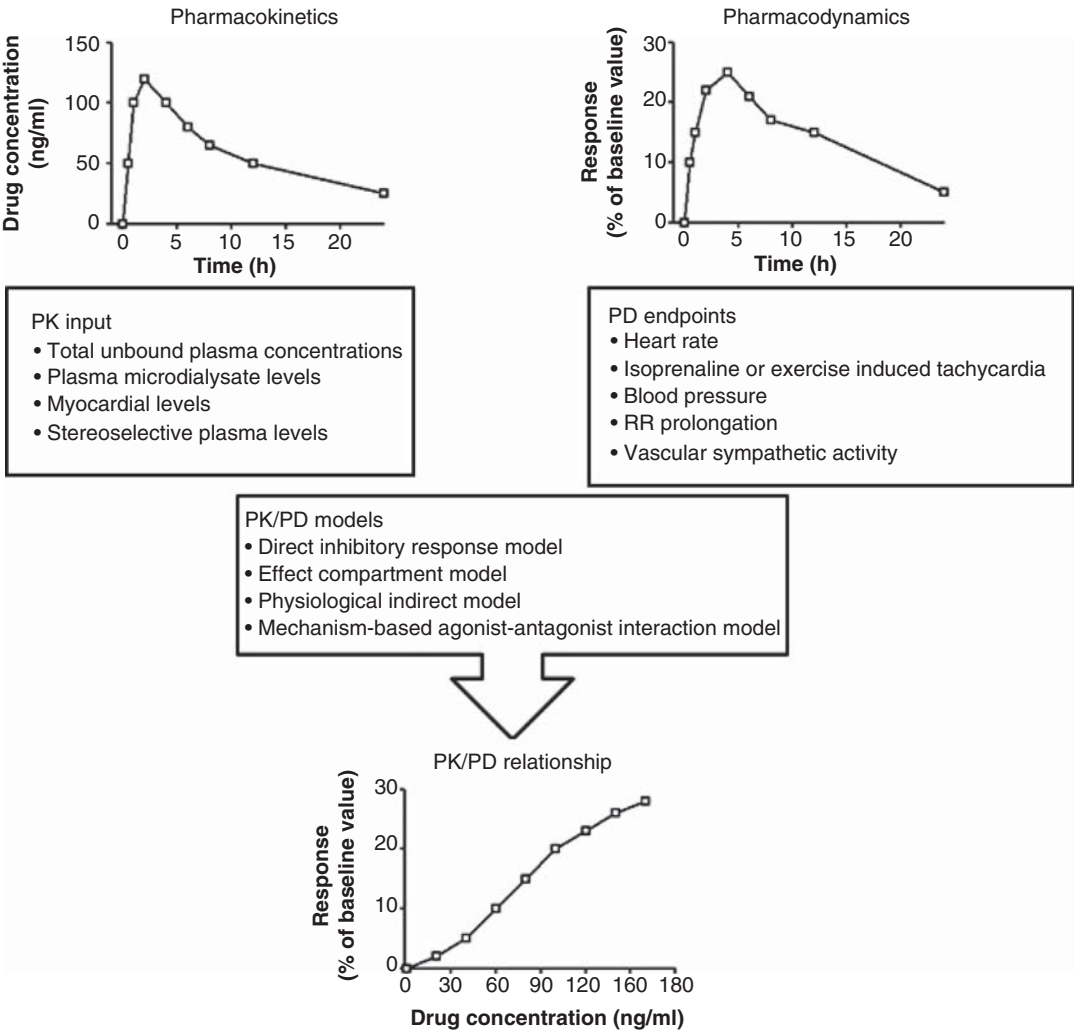

Figure 2. Design of PK/PD models for evaluation of cardiovascular response to β-blockers.
PD: Pharmacodynamic; PK: Pharmacokinetic.

levels and their effect on LF/HF ratio have been found in normotensive and hypertensive rats by means of PK/PD modeling [13].

The link between β-blocker tissue levels and their pharmacological response is established by the use of mathematical models, allowing the estimation of parameters such as EC_{50} and E_{max}. In the absence of temporal disconnection between tissue concentrations and pharmacological response, plasma concentrations of β-blockers can be directly related to cardiovascular effects using relatively simple PK/PD models (**Figure 3**) [51,52]. In this way, Tenero *et al.* have successfully applied a direct effect inhibitory model for the study of PK/PD parameters of carvedilol on exercise-induced heart rate reduction in patients with mild-to-severe heart failure or myocardial infarction with left ventricular dysfunction [66].

However, almost all PK/PD studies on β-blocker have described a delay in the onset of both chronotropic effect and blood pressure reductions with regards to plasma drug concentrations. In these cases, plasma concentrations cannot be directly linked to drug effect and more complex PK–PD models such as an effect-compartment model and a physiological indirect response model are needed (**Figure 3**). One possible explanation for the delay in the onset of cardiovascular action of β-blockers could be the time required for distribution of the drug in the biophase. The effect-compartment model considers a hypothetical effect compartment as an additional compartment of a PK compartment model, representing the drug concentration at the effect site [45]. Therefore, this PK/PD model considers that the time-dependent aspects of the equilibrium between plasma concentration and the effects are characterized by the first-order rate constant, K_{e0}, which represents the irreversible disappearance of the drug from the effect compartment [45]. This approach has been successfully applied to predict the

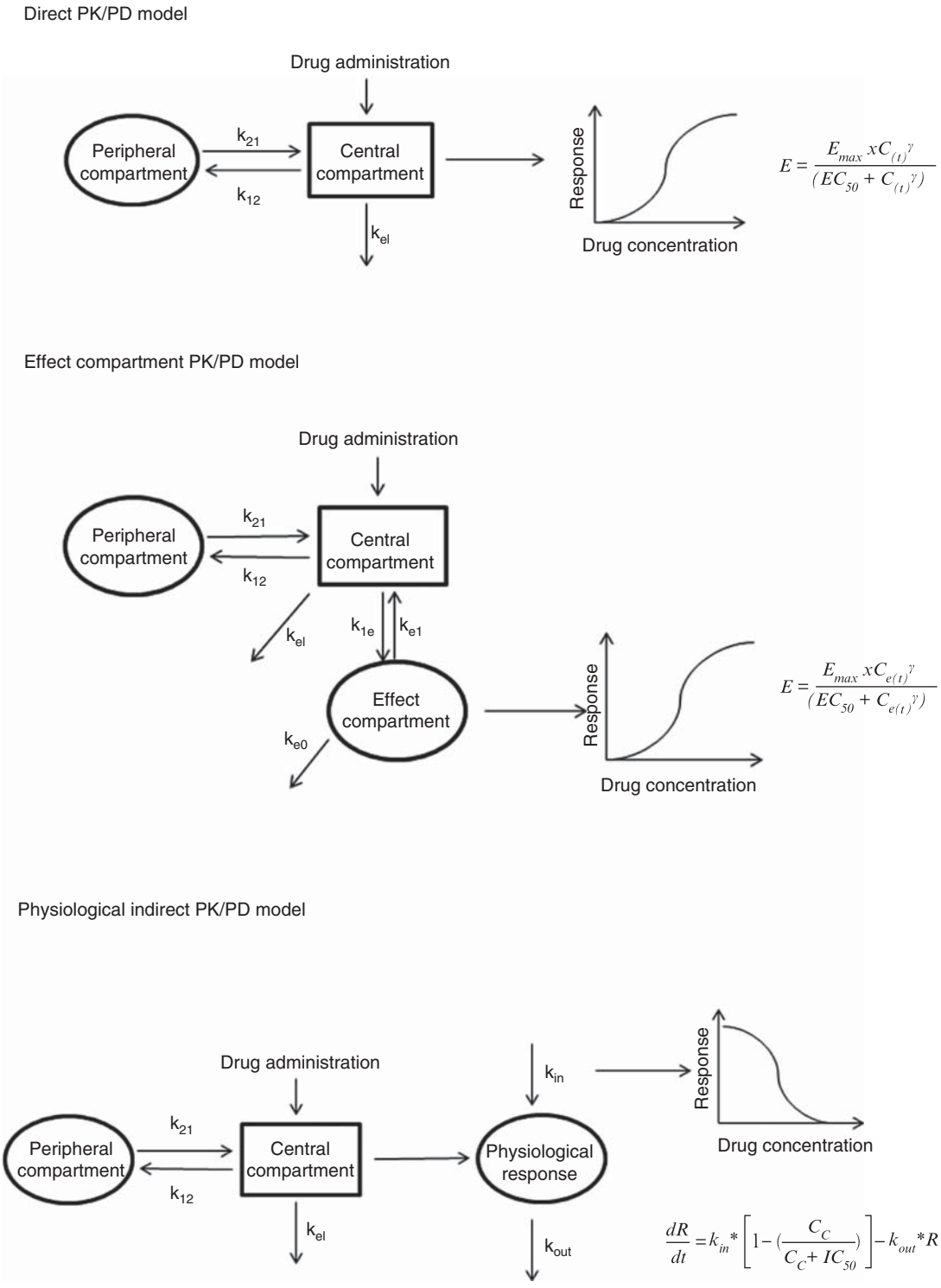

Figure 3. PK/PD models used for the study of β-blockers.

EC_{50}: Effective concentration to yield half-maximal response; E_{max}: Maximal efficacy; IC_{50}: Inhibition constant for 50% inhibition of maximum function of Kin; k_{12}: Rate transfer constant from the central to peripheral compartment; k_{1e}: Rate constant for transport through the effect compartment; k_{21}: Rate transfer constant from the peripheral to central compartment; k_{e0}: Rate constant for the loss from the effect compartment; k_{el}: Constant of loss from the central compartment; k_{in}: Zero-order production rate constant; k_{out}: First-order removal rate constant; PD: Pharmacodynamic; PK: Pharmacokinetic; R: Response.

PK/PD relationship of the chronotropic and hypotensive response to β-blockers.

A second explanation for the delay in the onset of cardiovascular effects of β-blocker could be the fact that the mechanism of action of these drugs involves inhibition of physiological process involved in the elaboration of the clinical expression of observed effect. For instance, vascular sympathetic tone is a physiological parameter constantly produced through zero-order kinetics (K_{in}) and removed in first-order kinetics with a rate constant K_{out} (**Figure 3**). In this case, third-generation β-blockers with α-adrenergic antagonist properties, such as carvedilol, inhibit the production of the sympathetic tone (inhibition of K_{in}), thereby affecting its magnitude [13]. A physiological indirect PK–PD model was successfully designed for the characterization carvedilol effects on LF/HF ratio in normotensive and hypertensive rats [13].

Considering the availability of different PK/PD models for the estimation of *in vivo* PD parameters, it is important to select the most adequate model by comparison of goodness of fit parameters. Liu and co-workers have compared the indirect response and the effect-compartment link model for the estimation of carvedilol effects on blood pressure measured by tail-cuff manometry in 20 male healthy Chinese volunteers [67]. According to the analysis of the Akaike's information criterion values, a goodness of fit parameter, the authors have found that the effect-compartment link model provided more appropriate and better-fitting PK/PD characteristics of the blood pressure lowering response of carvedilol than the indirect response model [67].

In the last years, mechanism-based PK/PD models have been developed with the effort to improved extrapolation and prediction properties of pharmacological actions of drugs. Mechanism-based PK-PD models are able to distinct between parameters for describing drug-specific and biological system-specific properties by containing specific expressions for the characterization of processes on the causal path between drug exposure and drug response [68]. The different terms included in the mechanism-based PK/PD model are target-site distribution, target binding, and activation and transduction. As chronotropic response to β-blockers in the isoprenaline-induced tachycardia model depends on drug competition by the β_1-adrenergic receptor, van Steeg *et al.* have developed a mechanism-based PK/PD model for the study of the interaction between isoprenaline and S-atenolol using a PD interaction model based on the operational model of agonism that describes the heart rate response based on the affinity of the agonist, the affinity of the antagonist, the efficacy, the maximal effect, the Hill coefficient, the concentrations of isoprenaline and atenolol, and the displacement of the endogenous agonist adrenaline [69]. The model designed by van Steeg *et al.* allows the estimation of the *in vivo* affinity of β-blockers for the β_1-adrenoceptor using heart rate as a biomarker for receptor binding [69].

More recently, Snelder *et al.* have developed a mechanism-based PK/PD model for the characterization of the effects of cardiovascular drugs with different mechanisms of action, including β-blockers, on the interrelationship between mean arterial pressure (MAP), cardiac output (CO) and total peripheral resistance (TPR) [70]. Considering that MAP = CO × TPR, the model includes two indirect physiological models to describe the time course of change in CO and TPR. In these equations, K_{in_CO} and K_{in_TPR} represent the zero-order production rate constants and k_{out_CO} and k_{out_TPR} represent the first-order dissipation rate constants of CO and TPR, respectively. In addition, two feedback constants are introduced in order to take into account the magnitude of the negative feedback of MAP on CO and TPR [70]. During the development of the novel mechanism-based PK/PD model, the authors consider that antihypertensive drugs selectively influence either CO or TPR and that all compounds influence the production rates of CO or TPR rather than the dissipation rates [70]. As β-blockers reduce stimulation of left ventricular contractility and heart rate induced by cardiac sympathetic activation, these agents are thought to influence the production rather than the dissipation rate [70]. The authors have reported that the developed mechanism-based PK/PD model can be used for the quantification and prediction of propranolol effects on blood pressure. The proposed model may predict the effects of a particular β-blocker on blood pressure based on preclinical data [70]. Although the mechanism-based PK/PD model seems to be suitable for the evaluation of cardiovascular actions of most β-blockers, it requires modifications for vasodilatory β-blockers, considering the fact that the blood pressure reduction induced by these agents depends not only from the effects on CO but also on TPR.

The duration of treatment represents another relevant factor to consider in the design of PK/PD studies of β-blockers. Relatively simple PK/PD models are needed to describe PK/PD relationships after multiple doses or long-term infusion, because the system is kinetically at steady state [52]. The most common mathematical equations employed in steady-state conditions are the linear, log linear and E_{max} models. Conversely, more complex PK/PD models are needed to describe the relationship between PK and PD after single-dose administration or when time dependency in the PDs of the drug is present [52]. On the other hand, it is a well known fact that hemodynamic changes induced by β-blockers can differ after administration of a single dose or multiple dosing [52]. Man in't Veld *et al.* have found that non-vasodilating β-blockers initially induce an increase in vascular resistance proportional to the fall in CO, although blood pressure always fell parallel with the decline in vascular resistance after multiple dosing [71].

3.2 Preclinical PK/PD models of β-blockers

Preclinical PK/PD models for β-blockers contributes to the elucidation of factors influencing cardiovascular response to these agents and increase the knowledge of their enantioselective PD properties and the relevance of sympathetic

Table 3. PK/PD models of β-blockers in preclinical studies.

β-blocker	Experimental subjects	PD end point	PK data	PK/PD model	Ref.
Atenolol	Conscious normotensive rats	Heart rate under isoprenaline-induced tachycardia	S-atenolol	Mechanism-based agonist–antagonist interaction model	[69]
Atenolol	Rabbits with renal failure	Chronotropic effect	Atenolol plasma levels	Effect-compartment model	[72]
Atenolol	Hypertensive rats	Hypotensive effect	Atenolol plasma levels	Effect-compartment model	
Carvedilol	Normotensive and hypertensive rats	Chronotropic effect	S-carvedilol plasma levels	Effect-compartment model	[11-13]
Carvedilol	Normotensive and hypertensive rats	Hypotensive effect	RS-carvedilol plasma levels	Effect-compartment model	[11-13]
Carvedilol	Normotensive and hypertensive rats	Sympathetic vascular activity	RS-carvedilol plasma levels	Inhibitory physiological indirect model	[13]
Metoprolol	Normotensive and hypertensive rats	Chronotropic effect	Racemic metoprolol unbound plasma levels	Effect-compartment model	[54,83]
Metoprolol	Normotensive and hypertensive rats	Hypotensive effect	Racemic metoprolol unbound plasma levels	Effect-compartment model	[54,83]
Metoprolol	Anesthetized dogs	Chronotropic effect	R- and S-metoprolol plasma levels	Effect-compartment model	[84]
Metoprolol	Hypertensive rats	Chronotropic effect	R- and S-metoprolol plasma levels	Effect-compartment model	[62]
Metoprolol	Rabbits with liver failure	Chronotropic effect	Racemic metoprolol plasma levels	Effect-compartment model	[73]
Metoprolol	Conscious normotensive rats	Heart rate under isoprenaline-induced tachycardia	S-metoprolol	Mechanism-based agonist–antagonist interaction model	[69]
Propranolol	Conscious normotensive rats	Heart rate under isoprenaline-induced tachycardia	S-propranolol	Mechanism-based agonist–antagonist interaction model	[69]

overactivity in the maintenance of the hypertensive stage (**Table 3**). By using an effect-compartment model, Celardo *et al.* [72] evaluated the influence of renal failure on the PK and PD profiles of atenolol in adult male rabbits on continuous peritoneal dialysis. The authors reported a nine-fold decrease of atenolol elimination and an increase in duration of drug effect during anuria [72]. Nevertheless, the blood concentrations of atenolol required to produce 50% of heart rate reduction was similar before and during renal failure, suggesting that reduction of kidney function alters the PK of atenolol without interference in their PD profile [72].

In another PK/PD study, Bortolotti *et al.* [73] have found that hepatic dysfunction affects *in vivo* PD properties of metoprolol. The authors evaluate the relationship between metoprolol plasma levels and their chronotropic effect by means of an effect compartment PK/PD model in adult male rabbits before and during liver failure [73]. Although hepatic dysfunction doubles the terminal elimination half-life of metoprolol when compared with normal liver function, chronotropic response induced by the β-blocker did not differ between both conditions [73]. Consequently, mean unbound plasma concentration producing 50% of heart rate reduction was doubled during liver failure compared to normal condition, suggesting a reduction of metoprolol potency associated with hepatic dysfunction [73].

The anesthesia seems also to affect the *in vivo* cardiovascular response to β-blockers. The chronotropic and blood pressure lowering effect of carvedilol have been studied in normotensive and NG-nitro-L-arginine methyl ester (L-NAME) hypertensive rats when they are awake or after intravenous anesthesia with urethane–chloralose [74]. Plasma carvedilol concentrations and changes in heart rate and blood pressure were continuously monitored. PK/PD parameters of carvedilol in both conditions were evaluated using an effect-compartment model [74]. Although anesthesia did not influence carvedilol concentration producing 50% of heart rate and blood pressure reduction, the use of urethane–chloralose increased maximal chronotropic and hypotensive response induced by the β-blocker [74].

On the other hand, mechanism-based PK/PD models allow the study of the influence of plasma protein binding on PDs of β-blockers. van Steeg *et al.* [69] compared the effects of four β-blockers (atenolol, propranolol, metoprolol and timolol) on heart rate under isoprenaline-induced tachycardia in conscious rats. Using a mechanism-based agonist–antagonist interaction model, the authors have found

Table 4. PK/PD models of β-blockers in clinical studies.

β-blocker	Experimental subjects	PD response	PK data	PK/PD model	Ref.
Atenolol	Healthy volunteers	Blood pressure reduction	Atenolol plasma levels	Effect-compartment model	[77]
Carvedilol	Healthy volunteers	Blood pressure reduction	RS-carvedilol plasma levels	Effect-compartment model and physiological indirect model	[67,77]
Carvedilol	Patients with mild-to-severe heart failure or myocardial infarction with left ventricular dysfunction	Exercise-induced heart rate reduction	S-carvedilol levels	Direct effect inhibitory model	[66]
Metoprolol	Patients undergoing diagnostic cardiac catheterization	Reduction in spontaneous heart rate, reduction in contractile index peak positive rate of left ventricular pressure rise, prolongation of PR interval	Myocardial metoprolol levels	Effect-compartment model	[85]
Metoprolol	Healthy volunteers	Heart rate and blood pressure reduction	Metoprolol plasma concentration	Direct effect inhibitory model	[75]
Labetalol	Pregnant hypertensive women	Blood pressure reduction	Labetalol plasma concentration	Direct E_{max} sigmoidal model	[78]

PD: Pharmacodynamic; PK: Pharmacokinetic.

that the *in vivo* estimates of receptor affinities diverges from the *in vitro* receptor affinity, particularly for the most highly bound drug S-propranolol [69]. Therefore, plasma protein binding influences PDs of β-blockers and the free plasma concentration appear to be the best predictor of *in vivo* drug potency [69].

PK/PD models also contribute to increase the knowledge of enantioselective PD properties of β-blockers and the relevance of sympathetic overactivity in the maintenance of the hypertensive stage. The PK and PD properties of carvedilol have been compared in L-NAME hypertensive rats and normotensive rats by means enantioselective PK/PD modeling. The relationship between carvedilol concentrations and their hypotensive and bradycardic effects was established using an effect compartment PK/PD model [13]. In addition, RS-carvedilol plasma concentrations and their effect on vascular sympathetic activity were established by means of a physiological indirect PK–PD model [13]. Although the PK–PD properties of the S-carvedilol chronotropic effect were not altered in L-NAME rats, hypertensive rats showed greater potency and efficacy to the carvedilol hypotensive response, which may be explained by the greater potency of carvedilol for sympathetic vascular tone inhibition [13].

3.3 Clinical PK/PD models of β-blockers

In the clinical setting, PK/PD modeling has been used for the prediction of PD properties of β-blockers in patients with hypertension, mild-to-severe heart failure and in subjects after myocardial infarction with left ventricular dysfunction (**Table 4**). Tenero *et al.* [66] compared the PD properties of IR and CR formulations of carvedilol in patients with cardiac dysfunction or post-myocardial infarction. The authors established the PK/PD relationship between S-carvedilol plasma concentrations and the change in exercise-induced heart rate was best described using a direct effect inhibitory E_{max} model [66]. The proposed model was able to predict the overall PD properties of IR and CR carvedilol. Moreover the area under the effect curve after CR carvedilol was equivalent than IR formulations, suggesting a 24-h β-blocking coverage for the CR formulation of carvedilol given once daily in patients with heart failure [66]. This study clearly demonstrates the utility of PK/PD modeling for the optimization of dose regimen of β-blockers in patients with heart failure.

In the clinical setting, Luzier *et al.* [75] described a good relationship between plasma concentrations of metoprolol and their effect on systolic blood pressure by means of a PK/PD model with an effect compartment. Moreover, in their report, the authors found that both maximal blood pressure lowering response and potency of metoprolol do not differ between men and women, concluding that the greater antihypertensive response to metoprolol in female subjects is due to gender-specific differences in metoprolol PKs [75].

PK/PD modeling of acebutolol has demonstrated the effects of age on PDs of β-blockers. Scott *et al.* have evaluated the effect of a single intravenous dose of acebutolol on heart rate and blood pressure by means of PK/PD modeling [76]. Compared to placebo, administration of acebutolol produced significant cardiovascular changes and PK/PD modeling

demonstrated a significant negative correlation between blood pressure lowering response to acebutolol and age [76].

Recently, PK/PD properties of the hypotensive effect of atenolol and carvedilol have been described in normotensive volunteers. PK/PD modeling of carvedilol and atenolol was successfully described by using an effect-compartment model, suggesting the existence of time delay between plasma drug concentration and its effect on systolic and diastolic blood pressure [77]. This study shows that PK/PD modeling allows the study of the existence of a time delay in the onset of the pharmacological effect of β-blockers optimizing time of antihypertensive drug dosing. It is well known that blood pressure varies according to the time of the day, rising rapidly in the morning upon awakening [51]. Therefore, time of dosing of antihypertensive drug is essential to improve treatment of hypertension. Nowadays, optimal time dosing of antihypertensive drugs is selected considering the PK profile of the drug rather than its blood pressure lowering response [51]. In the case of β-blockers, the delay in the onset of action determined by PK/PD modeling must be added to the delay in achieving maximal plasma concentration of these drugs after oral dosing in order to estimate optimal time of dosing [51].

In another PK/PD study, the relationship between labetalol plasma levels and the hypotensive response was described in pregnant women with moderate-to-severe hypertension by using a sigmoidal E_{max} model [78]. The authors found a three- to fivefold interindividual variability in the PD parameters E_{max} and EC_{50} of the hypotensive response to labetalol demonstrating the relevance of PK/PD studies for the evaluation of the variability in antihypertensive drug response and optimization of dose selection [78].

4. Conclusions

In conclusion, a wide variety of PK and PK/PD models have been developed to characterize the PK and PD properties of different β-blockers. The application of population PK models contributes to identify the factors associated to large interindividual variability in PK properties of β-blockers. On the other hand, PK/PD modeling has the potential to identify determinants of cardiovascular response of β-blockers allowing the early detection of poor responders and the optimization of dose regimen in their different indications.

5. Expert opinion

To date, PK models and PK/PD modeling have clearly contributed to the knowledge of classical β-blockers used in the treatment of major cardiovascular diseases. PK models have allowed the identification of factors affecting the bioavailability and elimination of β-blockers in order to optimize dosing of these agents in different patient populations. On the other hand, PK/PD models of β-blockers have been mainly studied in the preclinical setting, but in the last years there have been expanded for the evaluation of PD properties in patients. The introduction of PK/PD models in the clinical setting would greatly contribute to optimize the use of β-blockers in their different indications, taking into account that this strategy allows the study of determinants of variability in antihypertensive response, the early detection of poor responders or non-responders, the optimization of antihypertensive drug regimen, in terms of dose, sampling interval and time of dosing and the evaluation of the clinical impact of drug interactions [51].

In the future, PK and PK/PD models may be useful tools to compare the PD properties of the different available β-blockers. International guidelines on the management of hypertension and stable angina consider β-blockers as a homogenous therapeutic class, taking into account that the clinical benefit of β-blockers has been mainly attributed to the blockade of cardiac β-adrenoceptors, a pharmacological action shared by all β-blockers. In addition, important adverse effects associated with the treatment of β-blockers, including alterations in insulin sensitivity and lipid profile, are also related with the mechanism of action of β-adrenoceptors blocking agents [79,80]. In the last years, β-blockers were no longer considered as first-line therapy for hypertension due to suboptimal efficacy on reducing stroke events and increasing risk for new onset diabetes compared with other antihypertensive agents [80]. Three meta-analysis have found that β-blockers were less effective in reducing the composite end point of major cardiovascular outcomes, including stroke, myocardial infarction and death, compared to all other antihypertensive agents [79]. Several mechanisms have been suggested to explain the poorer ability of β-blockers to reduce cardiovascular events: a failure to decrease central aortic pressure, the propensity to cause diabetes and its neutral effect on blood pressure variability [79-81]. Nevertheless, it is important to mention that the primary β-blocker evaluated in the meta-analysis was atenolol, a cardioselective β-blocker without vasodilatory properties [79,80]. In addition, new onset diabetes have been described for atenolol, metoprolol and propranolol, all β-blockers without direct effects on vascular resistance [79].

It has been postulated that third-generation β-blockers with vasodilatory action, including carvedilol and nebivolol, exhibit improved cardiovascular properties due to reduced cardiac afterload and preload, lack of adverse effects on lipid and glucose and possible reversal of adverse arterial remodeling [80]. In addition, preclinical and clinical studies have documented that β-blockers with vasodilatory actions are able to reduce both central aortic pressure and short-term blood pressure variability to a greater extend than traditional β-blockers [65,80].

In this context, differences in cardiovascular properties between classical β-blockers and vasodilatory β-blockers, such as carvedilol and nebivolol, need to be further studied in preclinical and clinical studies in order to confirm the

clinical benefits of the new generation β-blockers. The design of clinical studies focusing on the comparison of PK/PD models between cardioselective β-blockers and vasodilatory β-blockers may contribute to further clarify the benefits of additional pharmacological properties in the treatment of cardiovascular diseases. In this way, the mechanism-based PK/PD model developed by Snelder *et al.* [70] seems to be able to clarify the importance of the reduction in TPR reduction induced by vasodilatory β-blockers in blood pressure lowering response of these agents. In addition, the design of PK/PD models for the evaluation of metabolic adverse effects of β-blocker may also contribute to clarify the cardioprotective potential of the different agents of this heterogeneous group [86].

Acknowledgements

CA Taira is Career Investigators from CONICET, Argentina.

Declaration of interest

Funding for this paper has been received from the University of Buenos Aires. The authors do not have any potential conflict of interest to declare.

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