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Quantifying pharmacodynamic interaction between atenolol and valsartan

Research Article

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Abstract: We used mathematical modeling in order to determine the pharmacodynamic relationship between antihypertensive drugs atenolol and valsartan, by evaluating their effects on heart rate (HR), systolic blood pressure (SP) and diastolic blood pressure (DP). A group of twelve healthy male volunteers received a single oral dose of 100 mg of atenolol and 160 mg of valsartan, both separately and in combination. Pharmacokinetic (PK), pharmacokinetic/pharmacodynamic (PK/PD) and pharmacodynamic (PD) systems were proposed and PD model of atenolol and valsartan concentration-time profiles and PK/PD model of blood pressure and heart rate effects after administration of single doses of atenolol and valsartan and their combination were constructed. Parameters of PD system, such as gain and mean effect time, were obtained by analysis of PK and PK/PD systems. Modeling of PK and PK/PD systems and their analysis to obtain the PD results could considerably change the view o treatment of individual diseases in terms of greater knowledge of pharmacokinetics and pharmacodynamics of drugs.

Keywords: *Atenolol • Blood pressure • Mathematical modeling • Pharmacodynamics • Pharmacokinetics • Valsartan*

1. Introduction

Both atenolol and valsartan are classified as drugs primarily used for reducing blood pressure and treating heart failure [1,2]. Atenolol is a widely used beta-blocker influencing the renin-angiotensin system. It results in decline of blood pressure due to reduced renin secretion and subsequent decrease in angiotensin II production [7]. Therefore, it is applicable for treatment of hypertension [4] and for prevention of angina [3] or stroke [4].

Valsartan is an antihypertensive drug and an antagonist blocking the angiotensin II type 1 receptor [8]. It is used for treating high blood pressure [2], congestive heart failure [5] and for improving survival following myocardial infarction [6].

Hill equation [9] as well as other types of equations (reviewed in [10]) are used by many pharmacokinetic/pharmacodynamic (PK/PD) models to describe the static and dynamic effects of drugs and nonlinear drug-receptor relationships. In comparison with these models, our study introduces a system approach to modeling of PK/PD interaction based on dynamic system theory [11,12] between antihypertensive drugs, their combination in relation with heart rate (HR), systolic blood pressure (SP) and diastolic blood pressure (DP), based on the data from study by Czendlik et al. [13]. PD system analysis is based on modeling of PK and PK/PD systems. The proposed models aim not only to "just curve fitting" discussed by Rosenbaum [14] of atenolol and valsartan measured time profiles, however to model of the system of organism behavior after administration of the drugs orally. This system approach is related to

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subsequent utilization in PD modeling of HR, SP and DP effects in humans.

2. Materials and methods

2.1. 2.1. Study design

The study design was carried out as prior [13]. Briefly, twelve healthy male adult volunteers (age: 23-46 years) participated in the study. An open-label, three-period, randomized, balanced-crossover, single-dose design with at least one-week washout period between treatments, was used. The study followed the tenets of the World Medical Association's Declaration of Helsinki, Venice and Hong Kong amendments 1983 and 1989, and Good Clinical (Research) Practice (GCP). The study protocol and the subject-informed consent forms were approved by a properly constituted ethical review board. Informed consent for each subject in writing form prior to the start of study procedures was obtained. After an overnight fast, the subjects received a single dose of either 160 mg of valsartan or 100 mg of atenolol alone, or in combination (atenolol + valsartan) according to the three-period study design. The doses were swallowed in the form of tablets or capsules with 200 ml tap water at room temperature. Blood samples were collected before dosing (0 h) and at 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after dosing. Consequently, blood samples were centrifuged for 5 min and the plasma was stored at -18 ºC. The determination of atenolol and valsartan plasma concentrations was performed using a high-performance liquid chromatographic method (HPLC), with fluorimetric and UV detection, respectively. For determination of plasma angiotensin II (ANG II) concentration and plasma renin activity (PRA), specific radioimmunoassays (CIS BIO International, Gif-sur-Yvette, France) were used. The HR and the blood pressure data were measured before the dosing, and 2, 4, 8, 12 and 24 h after dose administration with Dinamap monitor; model 1846 SX (Criticon, Tampa, Fl., USA). The blood pressure was measured by an automatic blood pressure monitor (Colin STBP-780 of Hayshi, Komaki City, Aichi, Japan) and the HR was detected by a telemetric system (Polar Electro, Finland) [13].

2.2. Analysis of systems

Three types of systems were proposed for the analysis: the first one is the PD system with the dose D as input and the effect E as the output, the second one is the PK/PD system with the concentration C as the input and the effect E as the output, and the third one is the PK system with the dose D as the input and the concentration C as the output (Figure 1).

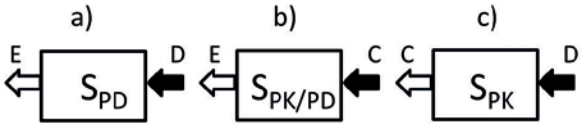

Figure 1. Single input single output systems. a) pharmacodynamic b) pharmacokinetic/ pharmacodynamic c) pharmacokinetic, C–measured concentration-time profile, D–dose, E–effect.

The main tools of mathematical modeling and analysis were based on the linear dynamic system theory [11, 12] with model parameters gain G, time constant T and time delay–a lag-time τ. Estimated parameter G describes the static properties of the system and derived parameter–mean time MT–defines the dynamic properties according to estimated parameters T and τ.

The gain of PK system G_{PK} was identified as

$$G_{PK} = \frac{1}{Cl} \text{ or } G_{PK} = \frac{AUC_C}{D}.$$

The gains $G_{PK/PD}$ of PK/PD system and G_{PD} of PD system were identified as

$$G_{PK/PD} = \frac{AUC_E}{AUC_C} \text{ and } G_{PD} = \frac{AUC_E}{D}, \text{ respectively,}$$

where Cl is clearance of the system, AUC is area under curve, C is drug concentration, D is drug dose, E is the effect, *i.e.* HR, systolic and diastolic blood pressure.

The PK model of dependence of atenolol and valsartan concentration-time profiles on drug doses administered separately or in combination, where its solution within the time area presents the Bateman function with a lag-time τ, was identified follows

$$C(s) = \frac{G}{(T_1.s+1).(T_2.s+1)} e^{-s\tau}.D \quad (1)$$

where G is gain of the subsystem, τ is a lag-time, T_1 and T_2 are time constants of the subsystems, *s* is Laplace operator, C and D are drug concentration and dose, respectively.

The total mean time of PK system is calculated as $MT_{PK} = \tau + T_1 + T_2$ where τ is time delay and T_1, T_2 are time constants of the subsystem.

The PK/PD model of dependence of HR, systolic and diastolic blood pressure effects from the concentration-time profile of atenolol and valsartan administered separately and/or in combination is identified as follows:

The PK/PD model of the heart rate HR^A as an output effect after atenolol administration and atenolol concentration C^A as an input to the system was identified as

$$HR^A(t) = G^A_{HR}.C^A(t) \quad (2)$$

where G^A_{HR} and C^A are gain and concentration of atenolol related to PK/PD system for HR, *t* is the time. The mean time MT^A_{HR} of PK/PD system for HR and atenolol administration is $MT^A_{HR} = 0$.

The PK/PD model of the heart rate HR^V as an output effect after valsartan administration and valsartan concentration C^V as an input to the system was identified as

$$HR^V(s) = \frac{G^V_{HR}}{T^V_{HR}s+1} e^{-s\tau^V_{HR}}.C^V(s) \quad (3)$$

where G^V_{HR}, τ^V_{HR} and T^V_{HR} are gain, time delay and time constant of valsartan of PK/PD system for HR, respectively. The mean time MT^V_{HR} of PK/PD system related to HR and valsartan administration is calculated as $MT^V_{HR} = \tau^V_{HR} + T^V_{HR}$.

The PK/PD model of heart rate ${}^{co}HR$ as an output effect after atenolol and valsartan combined administration, and atenolol ${}^{co}C^A$ and valsartan concentration ${}^{co}C^V$ as inputs to the system was identified as

$${}^{co}HR(t) = {}^{co}G^A_{HR}.{}^{co}C^A(t) + {}^{co}G^V_{HR}.{}^{co}C^V(t) \quad (4)$$

where ${}^{co}G^A_{HR}$ and ${}^{co}C^A$ are gain of PK/PD system for HR and concentration of atenolol administered in combination with valsartan, respectively. ${}^{co}G^V_{HR}$ and ${}^{co}C^V$ are gain of PK/PD system for HR and concentration of valsartan administered in combination with atenolol, respectively. ᶜᵒ means combined drugs administration. The whole gain ${}^{co}G_{HR}$ is calculated as ${}^{co}G_{HR} = {}^{co}G^A_{HR} + {}^{co}G^V_{HR}$. The mean time ${}^{co}MT_{HR}$ of PK/PD system for HR and drugs combined administration is ${}^{co}MT_{HR} = 0$.

The PK/PD model of the systolic blood pressure SP^A as the output effect after atenolol administration and C^A as atenolol input concentration to the system was identified as

$$SP^A(s) = \frac{G^A_{SP}}{T^A_{SP}s+1} C^A(s) \quad (5)$$

where G^A_{SP} and T^A_{SP} are gain and time constant of atenolol of PK/PD system for SP.

The PK/PD model of the systolic blood pressure SP^V as the output effect after valsartan administration and C^V as valsartan input concentration to the system was identified as

$$SP^V(s) = \frac{G^V_{SP}}{T^V_{SP}s+1} C^V(s) \quad (6)$$

where G^V_{SP} and T^V_{SP} are gain and time constant of valsartan of PK/PD system for SP.

The PK/PD model of the systolic blood pressure ${}^{co}SP$ as an output effect after atenolol and valsartan combined administration, and atenolol ${}^{co}C^A$ and valsartan concentration ${}^{co}C^V$ as inputs to the system was identified as

$${}^{co}SP(s) = \frac{{}^{co}G^A_{SP}}{{}^{co}T^A_{SP}s+1} {}^{co}C^A(s) + {}^{co}G^V_{SP}\,{}^{co}C^V(s) \quad (7)$$

where ${}^{co}G^A_{SP}$, ${}^{co}T^A_{SP}$ and ${}^{co}C^A$ are gain, time constant of PK/PD system for SP and concentration of atenolol administered in combination with valsartan, respectively. ${}^{co}G^V_{SP}$ and ${}^{co}C^V$ are gain of PK/PD system for SP and concentration of valsartan administered in combination with atenolol, respectively. The whole gain ${}^{co}G_{SP}$ is calculated as

$${}^{co}G_{SP} = {}^{co}G^A_{SP} + {}^{co}G^V_{SP}.$$

The mean times MT^A_{SP}, MT^V_{SP} and ${}^{co}MT_{SP}$ of PK/PD system for atenolol, valsartan and its combined administration for SP are equal to T^A_{SP}, T^V_{SP} and ${}^{co}T_{SP}$, respectively.

The PK/PD model of the diastolic blood pressure DP^A as the output effect after atenolol administration and C^A as atenolol input concentration to the system was identified as

$$DP^A(s) = \left(\frac{{}^1G^A_{DP}}{T^A_{DP}s+1} e^{-s\,{}^1\tau^A_{DP}} + {}^2G^A_{DP} \right) C^A(s) \quad (8)$$

where ${}^1G^A_{DP}$, τ^A_{DP} and T^A_{DP} are gain, time delay and time constant of atenolol of PK/PD system for DP, ${}^2G^A_{DP}$ is gain of the parallel subsystem. The whole gain G^A_{DP} is calculated as $G^A_{DP} = {}^1G^A_{DP} + {}^2G^A_{DP}$. The mean time MT^A_{DP} of PK/PD system related to HR and valsartan administration is calculated as $MT^A_{DP} = \tau^A_{DP} + T^A_{DP}$.

The PK/PD model of the diastolic blood pressure DP^V as the output effect after valsartan administration and C^V as valsartan input concentration to the system was identified as

$$DP^V(s) = \left(\frac{{}^1G^V_{DP}}{T^V_{DP}s+1} + {}^2G^V_{DP} \right) C^V(s) \quad (9)$$

where ${}^{1}G_{DP}^{V}$ and T_{DP}^{V} are gain and time constant of valsartan of one subsystem for DP, ${}^{2}G_{DP}^{V}$ is gain of the parallel subsystem. The whole gain G_{DP}^{V} is calculated as $G_{DP}^{V} = {}^{1}G_{DP}^{V} + {}^{2}G_{DP}^{V}$. The mean time MT_{DP}^{V} of PK/PD system related to HR and valsartan administration is calculated as $MT_{DP}^{V} = T_{DP}^{V}$.

The PK/PD model of the diastolic blood pressure ${}^{co}DP$ as output effect after atenolol and valsartan combined administration, and atenolol ${}^{co}C^{A}$ and valsartan concentration ${}^{co}C^{V}$ as inputs to the system was identified as

$$ {}^{co}DP(s) = \frac{{}^{co}G_{DP}^{A}}{{}^{co}T_{DP}^{A}s+1}\,{}^{co}C^{A}(s) + \frac{{}^{co}G_{DP}^{V}}{{}^{co}T_{DP}^{V}s+1}\,{}^{co}C^{V}(s) \quad (10) $$

where ${}^{co}G_{DP}^{A}$, ${}^{co}T_{DP}^{A}$ and ${}^{co}C^{A}$ are gain, time constant of PK/PD system for DP and concentration of atenolol administered in combination with valsartan, respectively. ${}^{co}G_{DP}^{V}$ and ${}^{co}C^{V}$ are gain of PK/PD system for DP and concentration of valsartan administered in combination with atenolol, respectively. The whole gain

${}^{co}G_{DP}$ is calculated as ${}^{co}G_{DP} = {}^{co}G_{DP}^{A} + {}^{co}G_{DP}^{V}$. The mean time ${}^{co}MT_{DP}$ is calculated as

$$ {}^{co}MT_{DP} = \frac{{}^{co}G_{DP}^{A}.\,{}^{co}T_{DP}^{A} + {}^{co}G_{DP}^{V}.\,{}^{co}T_{DP}^{V}}{{}^{co}G_{DP}^{A} + {}^{co}G_{DP}^{V}}. $$

Analysis of the measured data showed that PD system cannot be directly and mathematically modeled from atenolol and valsartan data because of a high measurement error of the effects after the oral administration to the human body, therefore parameters of PD system can be obtained by indirect way. Consequently, regarding separately administration of atenolol and valsartan, the gain of PD system G_{PD} is calculated by multiplication of the gains of the PK and PK/PD systems as follows

$$ G_{PD} = G_{PK} \,.\, G_{PK/PD} \quad (11) $$

In the case of atenolol and valsartan combined administration, the gain of PD system ${}^{co}G_{PD}$ is calculated as

$$ {}^{co}G_{PD} = {}^{co}G_{PK}^{A} \,.\, {}^{co}G_{PK/PD}^{A} + {}^{co}G_{PK}^{V} \,.\, {}^{co}G_{PK/PD}^{V} \quad (12) $$

where G_{PK} is gain of PK system, $G_{PK/PD}$ is gain of PK/PD system, A is atenolol, V is valsartan, ^{co} means combined administration.

The mean time of PD system MT_{PD}, in the case of separately administration of atenolol and valsartan, is calculated following

$$ MT_{PD} = MT_{PK} + MT_{PK/PD} $$

where MT_{PK} is mean time of PK system and $MT_{PK/PD}$ is mean time of PK/PD system.

The mean time of PD system ${}^{co}MT_{PD}$ for atenolol with valsartan combined administration is calculated as

$$ {}^{co}MT_{PD} = \frac{{}^{co}G_{PK}^{A}.\,{}^{co}G_{PK/PD}^{A}.\left({}^{co}MT_{PK}^{A} + {}^{co}MT_{PK/PD}^{A}\right) + {}^{co}G_{PK}^{V}.\,{}^{co}G_{PK/PD}^{V}.\left({}^{co}MT_{PK}^{V} + {}^{co}MT_{PK/PD}^{V}\right)}{{}^{co}G_{PK}^{A}.\,{}^{co}G_{PK/PD}^{A} + {}^{co}G_{PK}^{V}.\,{}^{co}G_{PK/PD}^{V}} $$

The model parameters were estimated by nonlinear regression analysis implemented in CTDB software (Clinical Trials Database) [15]. The point estimate by Monte Carlo method and the interval estimate by Gauss-Newton method were used. The minimal value of Akaike's information criterion was applied as the optimal model selection criterion [16].

3. Results

3.1. The results of PK modeling

The model estimated parameters of PK system for concentration of atenolol and valsartan administered separately and in combination are listed in Table 1 and Table 2, respectively.

Regarding the model estimated parameters listed in Table 1, the single doses of atenolol and valsartan are administered separately and present an input to the PK system (see Figure 1c).

In the case 1 listed in Table 2, the model identifies dependence of atenolol concentration on atenolol dose in situation when atenolol was administered in combination with valsartan. In the case 2, the model identifies dependence of valsartan concentration on valsartan

Table 1. The estimated model parameters of PK system for separately administered atenolol and valsartan single doses.

Drug	τ (h)	T_1 (h)	T_2 (h)	G (h/l)	MT (h)	AUC_C (mg.l)
Atenolol	0	4.887±1.15	1.794±0.49	0.0405±0.002	6.689±1.64	4.05
Valsartan	0.819±0.05	0.491±0.14	3.846±0.09	0.09469±0.0004	5.165±0.28	15.15

τ–lag-time; T_1, T_2–time constants of the subsystems; G–gain of the system; MT–mean time; AUC_C–area under concentration-time curve; ±–standard deviation.

Table 2. The estimated model parameters of PK system in two cases of combined administration of atenolol and valsartan single doses.

Case	τ (h)	T_1 (h)	T_2 (h)	G (h/l)	MT (h)	AUC_C (mg.l)
1	0	5.445±0.86	1.540±0.30	0.0613±0.003	6.985±1.16	6.13
2	0.892±0.79	0.167±>>	3.262±0.32	0.155±0.02	4.321±>>	24.8

Case 1–dependence of atenolol concentration on atenolol dose if atenolol was combined administered with valsartan; Case 2–dependence of valsartan concentration on valsartan dose if valsartan was combined administered with atenolol; τ–lag-time; T1, T2–time constants of the subsystems; G–gain of the system; MT–mean time; AUCC–area under concentration-time curve; ±–standard deviation.

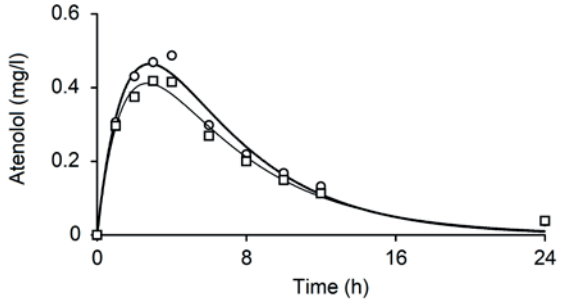

Figure 2. Concentration-time profile of atenolol administered separately and in combination with valsartan by PK model. Squares–measured concentration of atenolol administered separately; circles–measured concentration of atenolol administered in combination with valsartan; line–model approximation.

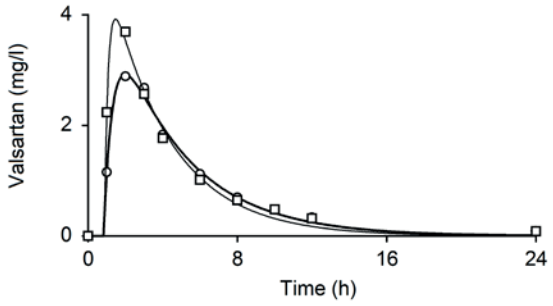

Figure 3. Concentration-time profile of valsartan administered separately and in combination with atenolol by PK model. Squares–measured concentration of valsartan administered separately; circles–measured concentration of valsartan administered in combination with atenolol; line–model approximation.

dose in situation when valsartan was administered in combination with atenolol.

Figures 2 and 3 describe the results of PK modeling of atenolol or valsartan concentration-time profiles according to Eq. 1. The input presents a single dose of atenolol or valsartan administered separately or in combination, and the output measures drug concentration in the case 1 or 2, respectively.

3.2. The results of PK/PD modeling

The model estimated parameters of PK/PD system for HR after separate administration of a single dose of atenolol (Eq. 2), valsartan (Eq. 3) and their combination (Eq. 4) are listed in Table 3.

The model estimated parameters of PK/PD system for SP after separate administration of a single dose of atenolol (Eq. 5), valsartan (Eq. 6) and their combination (Eq. 7) are listed in Table 4.

The model estimated parameters of PK/PD system for DP after separate administration of a single dose of atenolol (Eq. 8), valsartan (Eq. 9) and their combination (Eq. 10) are listed in Table 5.

Figures 4, 5 and 6 show the results of PK/PD modeling of HR (Eq. 2, 3, 4), systolic (Eq. 5, 6, 7) and diastolic blood pressure (Eq. 8, 9, 10), respectively, after

Table 3. The estimated model parameters of PK/PD system for HR after atenolol and valsartan administration separately (a) and in combination (b).

a)

Drug	τ (h)	T (h)	G (h.beats/min/mg/l)	MT (h)
Atenolol	0	0	-26.189±3.66	0
Valsartan	6.179±0.58	4.167±2.71	6.842±2.04	10.346±3.29

τ–lag-time; T, G and MT–time constant, gain and mean time of HR effect, respectively; ±–standard deviation.

b)

Drug	G^A (h.beats/min/mg/l)	G^V (h.beats/min/mg/l)	G (h.beats/min/mg/l)	MT (h)
A+V combined	-10.581±3.08	-0.167±0.44	-10.748±3.52	0

G^A, G^V- gains of the atenolol and valsartan subsystems; G and MT–gain and mean time of HR effect, respectively; ±–standard deviation.

Table 4. The estimated model parameters of PK/PD system for SP after atenolol and valsartan administration separately (a) and in combination (b).

a)

Drug	G (h.mmHg/mg/l)	MT (h)
Atenolol	-49.395±11.23	1.711±1.06
Valsartan	-7.025±2.09	2.921±1.76

G and MT–gain and mean time of SP effect, respectively; ±–standard deviation.

b)

Drug	G^A (h.mmHg/mg/l)	G^V (h.mmHg/mg/l)	G (h.mmHg/mg/l)	MT (h)
A+V combined	-52.487±7.76	0	-52.487±7.76	1.422±0.64

G^A, G^V- gains of the atenolol and valsartan subsystems; G and MT–gain and mean time of SP effect, respectively; ±–standard deviation.

Table 5. The estimated model parameters of PK/PD system for DP after atenolol and valsartan administration separately (a) and in combination (b).

a)

Drug	τ (h)	^1G (h.mmHg/mg/l)	T (h)	^2G (h.mmHg/mg/l)	G (h.mmHg/mg/l)	MT (h)
Atenolol	5.31±0.53	-35.088±4.96	12.920±3.44	-9.064±0.66	- 44.152±5.62	18.23±4.54
Valsartan	0	-7.075±0.58	7.397±5.65	-1.142±0.25	-8.217±0.83	7.397±1.89

τ–lag-time; G_1, G_2–gains of the subsystems; T, G and MT–time constant, gain and mean time of DP effect, respectively; ±–standard deviation.

b)

Drug	G^A (h.mmHg/mg/l)	T^A (h)	G^V (h.mmHg/mg/l)	T^V (h)	G (h.mmHg/mg/l)	MT (h)
A+V combined	-71.958±2.52	9.656±0.79	-2.100±0.71	0.448±0.15	-74.058±3.23	9.395±0.94

τ–lag-time; G^A, G^V- gains of the atenolol and valsartan subsystems; T^A, T^V–time constants of DP effect for atenolol and valsartan subsystems; G and MT–gain and mean time of DP effect, respectively; ±–standard deviation.

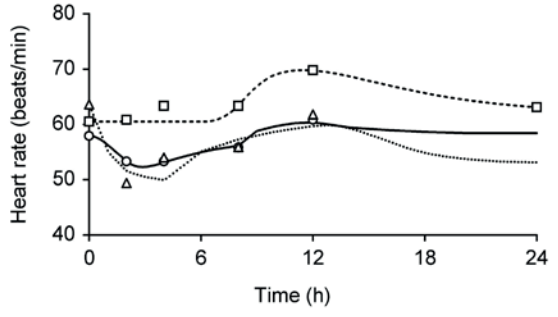

Figure 4. The PK/PD model solution of HR time profile related to measured atenolol (triangles), valsartan (squares) concentrations and their combination (circles).

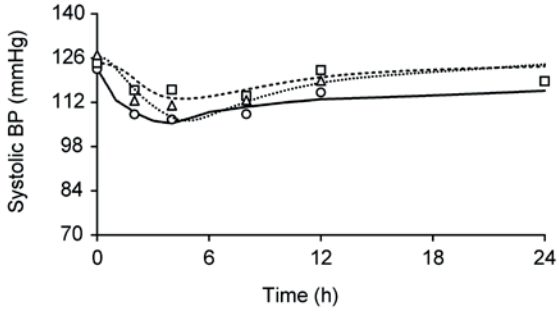

Figure 5. The PK/PD model solution of SP time profile related to measured atenolol (triangles), valsartan (squares) concentrations and their combination (circles).

separate and combined administration of atenolol and valsartan single doses.

3.3. The results of PD modeling

Tables 6 and 7 include the summary of parameters G and MT of PD system for HR, SP and DP after separate and/or combined administration of atenolol and valsartan.

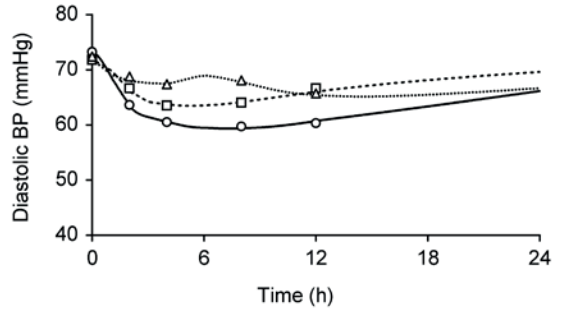

Figure 6. The PK/PD model solution of DP time profile related to measured atenolol (triangles), valsartan (squares) concentrations and their combination (circles).

Table 6. The parameters of PD system for HR after separate and combined administration of atenolol and valsartan.

Drug	G (h.beats/min/mg/l)	MT (h)
Atenolol	-1.061±0.74	6.689±1.64
Valsartan	0.648±0.63	15.511±3.57
combined	-0.674	6.883

G and MT- gain and mean time of HR effect; ±–standard deviation.

Table 7. The parameters of PD system for SP after separate and combined administration of atenolol and valsartan.

Drug	G (h.mmHg/mg)	MT (h)
Atenolol	-2.001±2.26	8.4±2.7
Valsartan	-0.665±0.64	8.086±2.04
combined	-3.217	8.407

G and MT- gain and mean time of SP effect; ±–standard deviation.

4. Discussion

The results of this study are quantified by model approach and comparable with results obtained by Czendlik et al. [13] who determined t_{max}, k_{el} and assessed AUC by using the linear trapezoidal method [13].

According to the PD results, reducing the HR was 36% less efficient after administration of atenolol + valsartan combined in comparison to single administration of atenolol. However, the mean effect time was 3% longer (see Table 6).

The study by Czendlik et al. [13] reports that combined administration of atenolol and valsartan does not have any additional impact on the HR. These PD results show a reduction in SP that is 60% more efficient if atenolol is administered in combination with valsartan than atenolol alone (Table 7). This supports the results from study by Czendlik et al. [13] that decreasing the level of SP is performed by combining atenolol and valsartan. The mean effect time is 8.41h atenolol and valsartan are administered together and that is similar to the case of single dose of atenolol (Table 7). As seen in Table 4b, the valsartan in combined administration with atenolol was not applicable in PK/PD model for SP, *i.e.* $^{co}G_{SP}^{V} = 0$, however caused an increase of atenolol gain $^{co}G_{SP}^{A}$ by 6%. This influenced our PD results for SP.

Table 8. The parameters of PD system for DP after separate and combined administration of atenolol and valsartan.

Drug	G (h.mmHg/mg)	MT (h)
Atenolol	-1.788±1.13	24.919±6.18
Valsartan	-0.778±0.641	12.562±2.17
combined	-4.736	15.825

G and MT- gain and mean time of DP effect; ±–standard deviation.

Presented PD results show that the decrease in DP is 165 % more efficient if atenolol is administered in combination with valsartan than atenolol administered alone (Table 8). This is in accordance with finding by Czendlik et al. [13] that the drop in DP is particularly evident after the combined administration of atenolol and valsartan. The mean effect time is 15.825 h if atenolol and valsartan are administered together and that is 36% shorter than in case of single dose of atenolol (Table 6).

As for the pharmacokinetic results, area under the concentration curve was calculated from the model parameters according to the following equation: $AUC = G_{PK}.D$, where G_{PK} is gain of pharmacokinetic system and D is dose, while Czendlik et al. assessed AUC by using the linear trapezoidal method [13]. According to our results, AUC for atenolol was 4.05mg.h/l. It is similar to Czendlik et al. result, 4.82 mg.h/l [13]. Study by Najib et al. [17] compared two brands of atenolol, Tensotin and Tenormin. The value of AUC for Tensotin was 6732.83 ng.h/ml (6.732 mg.h/l) and AUC for Tenormin 5963.14 ng.h/ml (5.963 mg.h/l). Input dose in both of the studies was 100 mg and the values are quite similar. Further supporting results are reported in the study of Spahn et al. [18] where AUC for atenolol was 5753.2ng.h/ml (5.753 mg.h/l) at an input dose of 100 mg. The study by Wu et al. [19] analyzed two atenolol products, Ateol and Tenormin. AUC for Ateol was 8.74 mg.h/l and for AUC for Tenormin was 7.88 mg.h/l. These values are markedly high compared to our results, despite similar number of volunteers and the input dose.

Our results show that AUC for valsartan was 15.15 mg.h/l. This is in accordance with a study by Czendlik et al., reporting that AUC was 17.81mg.h/ml. In a study of healthy volunteers by Spínola et al. [20], AUC for valsartan was 2374 ng.h/ml (23.749 mg.h/l). Compared with our results, this value is approximately 34% higher. This value is similar to our calculated AUC value for valsartan administrated in combination with atenolol (24.8 mg.h/l).

Input dose was 160 mg of valsartan in both of the studies, so this may be due to the limited number of volunteers involved in our study (12 volunteers compared to 42 volunteers in study by [20]). Zakeri-Milani et al. [21] reported more similar results of AUC for valsartan – 19172.2 ng.h/ml (19.172mg.h/l), though the volunteers were administered 80 mg of valsartan. The most similar results were obtained by Sioufi et al. [22]. According this study, AUC of valsartan was 16.1 mg.h/l in the group of healthy volunteers aged 18-28, even though the input dose was 80 mg.

5. Conclusion

The combined administration of atenolol and valsartan was most effective in reducing both the systolic and diastolic blood pressure. In comparison with previous studies, we are capable of determining the parameters of PD system as mean effect time and gain using the PK and PK/PD systems analysis. Modeling of PK and PK/PD systems and subsequently obtaining PD results contributes to better understanding of the drug's pharmacokinetics and pharmacodynamics as a tool in helping to treat individual diseases. It should be noted that only limited number of healthy volunteers participated in the study. In case of patients with malfunctioning renin-angiotensin system, as well as cardiovascular system, the final PK/PD concentration time-profiles, and consequently the PD results could be different. Developed models could be used also for verification of accuracy of the measurements of individual values in patients and for verification of supposed drug kinetics and pharmacodynamics related to the individual studies. The proposed modeling could play an important role mainly in bioequivalence tests and registration of new drugs, generics.

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