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Influence of Captopril Treatment of Plasma Renin Activity - Mathematical Model

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Abstract

A model of the dynamics of plasma renin activity under the influence of various doses of captopril is formulated. The influence of captopril on renin angiotensin system is different from the effects of the other studied drugs – nifedipine and nicardipine. Captopril inhibits the feedback in renin-angiotensin system and the upward trend of the renin activity is a proportional of the intrinsic growth rate. This dependence can be described using a modified Verhulst logistic function is proposed. The model is identified using the Korelia-Dynamics program. As optimization method for data identification a cyclic coordinate descent method is used. The residuals between the experimental data and the identified model are minimized applying least square or uniform fitting. The model allows prediction the effects of different captopril doses and permits the researcher to study the behavior of the renin angiotensin system under variety of conceivable conditions.

Keywords: plasma renin activity, renin angiotensin system, mathematical model, system identification

Introduction

The renin angiotensin system (RAS) is a fundamental regulating mechanism of the body fluids, electrolyte homeostasis and the arterial pressure (Atlas, 2007). The stimulation and inhibition of this multi-component system involve multiple negative feedbacks between the different links. The later feedbacks have the capacity to modulate in a complex fashion the quality of regulation of the synthesis and the secretion of every participating element on molecular level (Della Bruna *et al*., 1996; Ried, 1998). The major indicator of the condition of the system reflecting the equilibruim between the secretion and the degradation of renin is the plasma renin activity (PRA). When the equilibruim is moved in the direction of increased secretion and increased activity of renin the result is increased plasma concentration of angiotensin II. The later due to activation of a negative feedback inhibits the secretion of renin aiming to recover the equilibrium (Johns, 1990; Shricker *et al*., 1997) (Fig. 1).

The feedback mechanisms affecting renin are discussed in detail in (Xiao, 1997; Tolekova and Yankov, 2002).

Drugs such as nicardipine and nifedipine increase renin secretion (Tolekova *et al*. 1998; Tolekova and Yankov, 2002). During the experiment this reflects in growing of PRA. Therefore the growth of PRA after application of these two drugs speeds up (Fig. 2).

After their metabolism follows renin, respectively PRA decrease. Hence, the most appropriate mathematical model connecting the PRA with the levels of these two drugs is a second order ordinary differential equation. Tolekova and Yankov (2006) describe the mathematical model of PRA after nicardipine treatment and the model after nifedipine treatment in (Tolekova and Yankov, 2008).

Captopril is a widely used antihypertensive drug that inhibits ACE, the enzyme that converts angiotensin I to angiotensin II. This way it breaks the feedback, which influences renin secretion (Johns *et al*. 1990). The real growth rate of renin is a proportion of the intrinsic growth rate. This proportion however decreases with an increase in the quantity, leading to a more realistic scenario of a system that remains within bounds. The same natural law is valid in the process of angiotensin I degradation. Therefore, the upward and downward trends of PRA graphics for the captopril are approximately symmetrical. The different pharmacological mechanism of captopril effects in comparison with nicardipine and nifedipine necessitate a different mathematical model.

The purpose of this work was to formulate a model of PRA dynamics under the influence of different doses of captopril.

Materials and methods

1. Data acquisition

The experiments were carried out on 140 male white Wistar rats, divided into 4 experimental groups each of 25 animals. Each group was administered captopril in doses accordingly 10, 30, 60, 80 mg/kg body weight (b.w.) p.o. The administration of the drug was performed at 8:00

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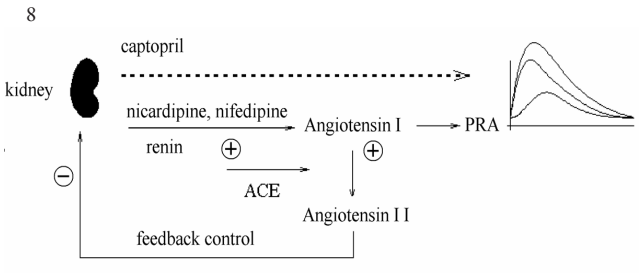

Fig. 1. Renin – angiotensin regulating system

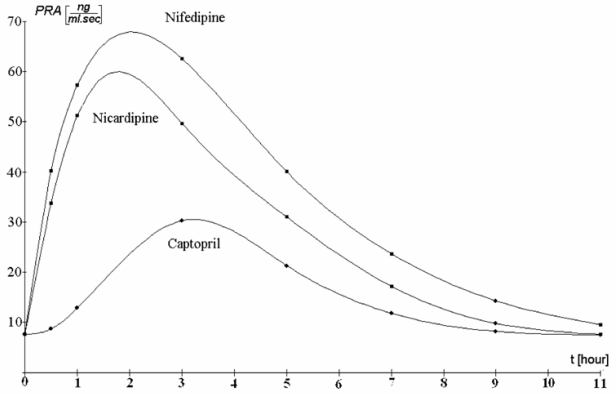

Fig. 2. PRA after treatement with dose 60mg/kg b.w.

a.m. After that the main groups were divided further to 5 subgroups depending of the time of blood collection. Each subgroup was made of 5 animals. The blood samples were collected intracardially after exsanguination under anesthesia with Nembutal in dose 50 mg/kg body weight (b.w.) accordingly on the 30 min, 1st, 3rd, 5th, and 7th hours after application of captopril. The control group was treated with the appropriate volume of saline per os. The values of experimental groups were compared with these of control group (n=18). A single sample was taken from each animal. The blood was centrifugated after which the plasma was decanted and preserved at -20°C untill the moment of radioimmunological determination of PRA. PRA was assessed radioimmunologicaly with assay of Dia-Sorin-Biomedica Ltd. Each sample determination was duplicated. The animals received human care and the study was complient with the Institution's guidelines of Trakia University and with the National rules and European regulatory rules: Decree for protection and human care of experimental animals №25/10.06.2005, Law of veterinary medical activities G87/11.01.2005, Atr 2(152 and 153) and Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes.

2. Design of the mathematical model

The model is determined from measured signals using identification method and software described in (Yankov, 2006). The identification follows the algorithm used in (Tolekova and Yankov, 2006; Tolekova and Yankov, 2008) too.

Input signal U(t). A short perorally application of captopril is considered as Dirac function. The signal amplitude is correlated to the captopril dose.

Output response y(t). During the experiment discrete-time output $\Phi(t) \subset y(t)$ is observed:

$$\mathbf{\Phi(t)} = [\phi_1, \phi_2, \ldots \phi_N,]^T, \text{ where N - number of samples.}$$

The measured data corresponding to **Φ(t)** are in Tab. 1. Vector **Φ(t)** is used during the identification process. The data in Tab. 1 are statistically processed using software Statistica 6 for Windows (StatSoft Inc).

Identification time t_p. The maximal duration time was fixed to 11 hours.

Sampling time. The first two samples were taken at 30 min and 1 hr and the subsequent - at every two hrs (Tab. 1).

Tab. 1. Plasma renin activity [ng/ml/h] presented as means and standard deviation

T	Dose [mg/kg] b.w.			
[hours]	10	30	60	80
0	7.58±0.8	7.58±0.8	7.58±0.8	7.58±0.8
0.5	7.9±0.7	8.3±0.8	8.7±0.4	9.1±1.3
1	9.8±1.1	10.7±0.2	12.9±0.4	13.8±1.2
3	20.7±1.6	25.1±2.5	30.3±0.7	32.6±1.7
5	15.1±0.9	17.7±2.2	21.3±1.6	22.3±2.1
7	8.6±0.7	10.1±0.9	11.8±0.5	12.5±1.4
9	7.6±0.9	7.6±0.7	8.2±1.1	8.5±0.8
11	7.6±0.6	7.5±0.7	7.5±0.9	7.8±0.7

3. Determination of the system model

This stage of identification includes the selection of mathematical equations from a set of candidate system descriptions within which a model is to be found.

A good mathematical model of this scenario is the Verhulst - Pearl equation. It has well served the description of growth for such processes as species occupying ecological niches, products occupying market niches, and knowledge accumulating according to learning curves. The Verhulst model is a differential equation, which relates the change in quantity size over time (to what; relate to or substitute with describes):

$$\frac{dy(t)}{dt} = r\left[1 - \frac{y(t)}{K}\right]y(t) \qquad (1)$$

- ***y(t)*** is the examined quantity at time ***t***;
- ***r*** is the growth rate;
- ***K*** is the carrying capacity. The parameter ***K*** is a measure of the available resources. If a quantity reaches the size ***K***, then all resources are used to keep the quantity level at ***K*** and no further growth is possible.

The solution ***y(t)*** of Eq.1 is a logistic function (or logistic growth model):

$$y(t) = \frac{K}{1 - \left(1 - \frac{K}{y(0)}\right) e^{(-r^* t)}} \qquad (2)$$

where $y(0)$ is initial quantity at time $t_0 = 0$.

In order to model the approximate symmetry of the graph, we use two simultaneous processes:

The first process $y_1(t,d)$ describes the growth of PRA and the restriction K_1 depends on the applied captopril dose:

$$\frac{d\, y_1(t,d)}{d\, t} = r_1(d)\left[1 - \frac{y_1(t,d)}{K_1(d)}\right] y_1(t,d) \qquad (3)$$

The solution is:

$$y_1(t) = \frac{K_1}{1 - \left(1 - \frac{K_1}{y_1(0)}\right) e^{(-r_1 * t)}} \qquad (4)$$

The second process $y_2(t,d)$ describes the decrease of PRA and the restriction K_2 is the angiotensin I exhaustion:

$$\frac{d\, y_2(t,d)}{d\, t} = -r_2(d)\left[1 - \frac{y_2(t,d)}{K_2(d)}\right] y_2(t,d) \qquad (5)$$

The solution is:

$$y_2(t) = -\frac{K_2}{1 - \left(1 - \frac{K_2}{y_2(0)}\right) e^{(-r_3 * t)}} \qquad (6)$$

Thus the model of PRA changes are described as a superposition of the two mentioned processes:

$$y(t,d) = y_1(t,d) + y_2(t,d) + A_d(d)$$

where $A_d(d)$ is the resting level of PRA.

Because there are analytical solutions (Eq.3 and Eq.4), it is more convenient to perform the identification using these solutions. In this case, the numerical integration of equations (3) and (5) is avoided during the identification process. That simplifies the calculations and reduces the identification time.

Following these considerations, for identification of PRA after captopril treatment, the proposed analytical model is:

$$y(t,d) = \frac{K_1(d)}{1 - \left(1 - \frac{K_1(d)}{y_1(0)}\right) e^{-r_1(d)*d}} - \frac{K_2(d)}{1 - \left(1 - \frac{K_2(d)}{y_2(0)}\right) e^{-r_2(d)*d}} + A_d(d) \qquad (7)$$

where:

$K_1(d)$	Maximal reached PRA depending on dose d;
$y_1(0)=7.58$	PRA at initial moment;
$r_1(d)$	PRA growth rate;
$K_2(d)$	The quantity of PRA to be subject to decrease. In the ideal case $K_1(d) = K_2(d)$;
$y_2(0)$	Conditional quantity of PRA at initial moment for decreasing process;
$r_2(d)$	PRA decrease rate;
$A_d(d)$	Resting level of PRA.

The significance of this model is the idea that the carrying capacity can be influenced by captopril availability.

The parameters above must be calculated in order to identify the process. All of them are dose (**d**) dependent and they form the identification vector **Q(d)**:

$$Q(d)=Q(K_1(d), r_1(d), K_2(d), r_2(d), y_2(0), A_d(d))$$

The mathematical model is identified using the Korelia-Dynamix program (Yankov, 2006). Korelia-Dynamix identifies algebraic, transcendental and ordinary differential equations. The proper model is recognized analysing input data (Yankov, 2009) or is introduced using specialized description language (Yankov, 2008). As identification method is applied the cyclic coordinate descent method (CCD). The residuals between experimental data and identified model are minimized applying least square or uniform fitting.

Results

The calculated values of the $\mathbf{K_1(d)}$, $\mathbf{r_1(d)}$, $\mathbf{K_2(d)}$, $\mathbf{r_2(d)}$, $\mathbf{y_2(0)}$ and $\mathbf{A_d(d)}$ are presented in Tab. 2.

Tab. 2. Identification parameters for Eq. 7

parameters	Dose [md/kg] b.w.			
	10	30	60	80
$K_1(d)$	75.41	93.64	119.36	124.54
$r_1(d)$	0.972	1.026	1.120	1.125
$K_2(d)$	72.88	91.813	115.96	121.818
$y_2(0)$	5.17	5.17	5.17	5.17
$r_2(d)$	0.8092	0.8500	0.9365	0.9400
$A_d(d)$	4.479	4.700	4.9383	5.064

10

The parameters $\mathbf{K_1(d)}$, $\mathbf{K_2(d)}$ (Fig. 3), $\mathbf{r_1(d)}$, $\mathbf{r_2(d)}$ (Fig. 4) and $\mathbf{A_d(d)}$ (Fig. 5) are nonlinear in relation to the captopril dose **d**. They must be identified as a function of the dose. The dependence of the change of the parameter on the applied dose can be modeled with exponential growth curve of the type:

$$F(d) = C_\infty \left[1 - e^{-\left(\frac{d}{D}+\Delta\right)} \right] + C_{const}, F(d) \in Q(d) \qquad (8)$$

The unknown parameters for identification are:

Applying again the CCD, the calculated values for identification parameters are in Tab. 3.

$C_\infty = F(\infty)$
D – dose-constant
Δ - dose correction parameter
C_{const} – free term

Tab. 3. Identification parameters for Eq. 8

F(d)	parameters			
	C_∞	D	Δ	C_{const}
$K_1(d)$	121.575	35.714	0.4546	8.8180
$r_1(d)$	1.099	48.780	1.3910	0.0868
$K_2(d)$	119.999	32.258	0.4722	4.7338
$r_2(d)$	1.1428	60.976	1.4540	-0.1182
$A_d(d)$	0.348	84.746	1.2011	5.1638

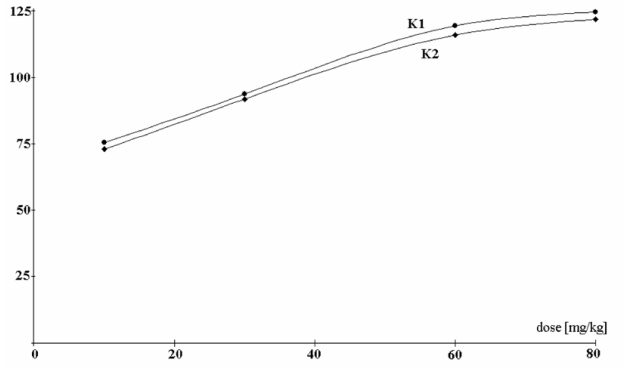

Fig. 3. Carrying capacities $K_1(d)$ and $K_2(d)$

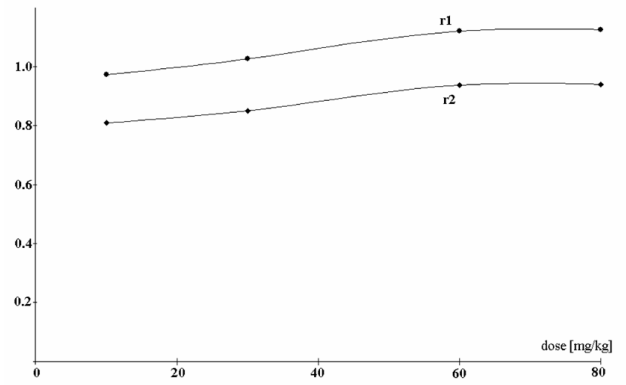

Fig. 4. Growth rate $r_1(d)$ and decrease rate $r_2(d)$

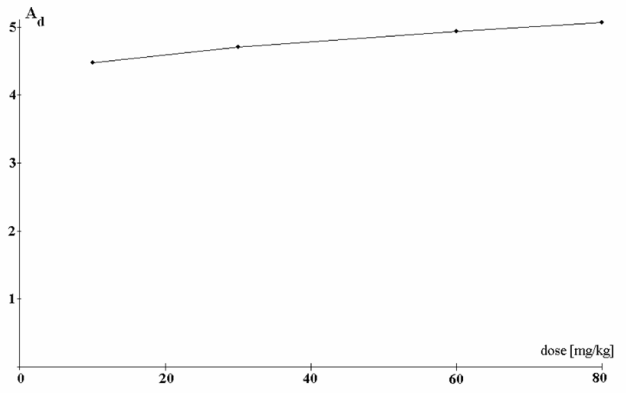

Fig. 5. Resting level $A_d(d)$

Finally, the time and dose dependent PRA model is described by the system of equations:

$$K_1(d) = 130.3930 - 121.575e^{-\left(\frac{d}{35.714}+0.4546\right)}$$

$$r_1(d) = 1.1858 - 1.099e^{-\left(\frac{d}{48.780}+1.3910\right)}$$

$$K_2(d) = 124.7328 - 119.999e^{-\left(\frac{d}{32.258}+0.4722\right)} \qquad (6)$$

$$r_2(d) = 1.0246 - 1.1428e^{-\left(\frac{d}{60.976}+1.4540\right)}$$

$$A_d(d) = 5.5118 - 0.348e^{-\left(\frac{d}{84.746}+1.2011\right)}$$

$$y(t,d) = \frac{K_1(d)}{1-\left(1-\frac{K_1(d)}{7.58}\right)e^{-r_1(d)*d}} - \frac{K_2(d)}{1-\left(1-\frac{K_2(d)}{5.17}\right)e^{-r_2(d)*d}} + A_d(d)$$

The graphs of the experimental data interpolated using cubic spline and the generated models of PRA for dose of 10 and 60 mg/kg are shown on Fig. 6, and the correspon-

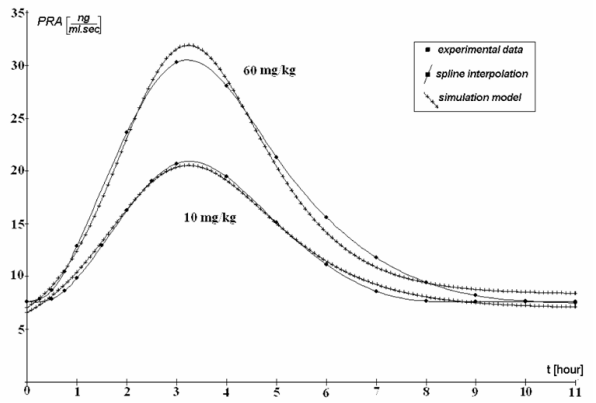

Fig. 6. Experimental data and simulation model for doses 10 and 60 mg/kg b.w.

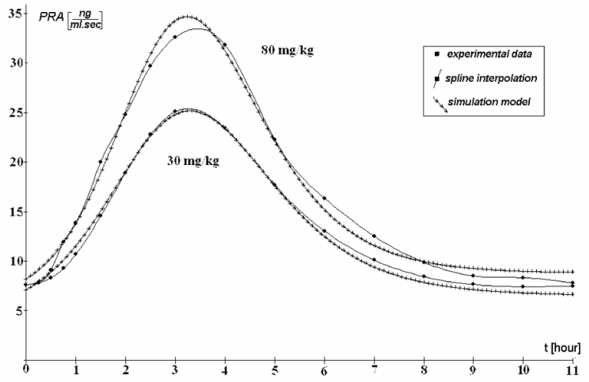

Fig. 7. Experimental data and simulation model for doses 30 and 80 mg/kg b.w.

dent graphs for dose of 30 and 80 mg/kg are shown on Fig. 7.

Discussion

The coefficient K_1 is greater than K_2 for all applied doses of captopril. The significance of this result is that the whole quantity of angiotensin I present after the blockage is not degraded completely in order to be eliminated from the blood stream. This phenomenon was not established with the trivial methods of investigation. The explanation of the obscurity of that process can be found in the enzymatic nature of renin, which obviously is much more active than the nonspecific enzymes, which degrade angiotensin I without converting it to angiotensin II. In that case there is a positive metabolite balance of the angiotensin I (the production rate is greater that the degradation rate) which leads to substrate accumulation. When the substrate reaches a certain quantity is could escape the blockage of angiotensin-converting enzyme. The advantage of mathematical modeling is that the results point our attention to a process which is not well elucidated but which is important to the effective medication with angiotensin-converting enzyme blockers.

When the change of r_1 and r_2 is followed, a similar tendency is found. The two coefficients change in a parallel manner with the value of r_1 always bigger than the one of r_2. This tendency speaks that more angiotensin I is synthesized than is degraded which reflects upon steeper upward shoulder and gentle downwards shoulder of the graph of the change of PRA with time.

Conclusions

In this paper, we derive an analytical model of plasma renin activity after captopril treatment. Captopril inhibits the feedback in RAS and the upward trend of the renin is a proportional of the intrinsic growth rate. For that reason the sistem is modeled with a modified logistic model.

With the help of our model we establish that angiotensin I is not degraded completely. This fact justifies more extensive pharmacological and physiological investigation of the processes in the human body connected to the interactions of the non-degraded angiotensin I.

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