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DOSE-DEPENDENT BIFURCATION ANALYSIS OF PLASMA RENIN ACTIVITY AFTER NICARDIPINE TREATMENT

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Abstract: *Renin-angiotensin system is one of the general regulatory mechanisms of blood pressure. The activity of the system depends on the rate of renin secretion, therefore, plasma renin activity (PRA) is one of the main variables that mediates the effect of a number of factors on blood pressure. Consequently, the impact of a particular drug on blood pressure disorders can be evaluated by the PRA changes. In clinical practice, the administered therapeutic dose is of critical nature, and a number of methods are known for its calculation. In the present study, applying bifurcation analysis the range of the administered doses of the nicardipine (antihypertensive drug) are determined. The bifurcation diagrams show how the stability of the renin-angiotensin system depends on the administered dose.*
Keywords: *Bifurcation, Phase Plane, Plasma renin activity, Stability analysis, Modeling.*

“That which is static and repetitive is boring. That which is dynamic and random is confusing. In between lies art.” John A. Locke (1632–1704), British philosopher and medical researcher

1. INTRODUCTION

The regulation of blood pressure in the body is carried out by the renin-angiotensin system. The criterion for its action is plasma renin activity (PRA). The effect of a particular drug on blood pressure abnormalities can be evaluated by monitoring the change in PRA. Therefore, one of the approaches to drug regulation of blood pressure is the impact on PRA. This can be done by administering various drugs: calmodulin inhibitors [2], prostaglandin synthase blockers [4], angiotensin-converting enzyme inhibitors [5] and calcium channel blockers [8]. In all cases, the dosage of the drug is important [9,10]. A significant problem with medication administration is to investigate how the stability of the physiological system is affected by the drug. When the reaction depends on a parameter, in this case, the dose administered, it is advisable to determine critical values for that parameter at which the system would dramatically change its behavior. Bifurcation analysis shows the behavior of a system as a function of a selected parameter [1].
In the present work with the means of bifurcation analysis, the critical limits of the administered doses of the preparation nicardipine are determined. The bifurcation diagrams show how the stability of the renin-angiotensin system depends on a given parameter, in this case, the dose administered. Predicting the required dose of the drug makes it possible to avoid the side effects of the body.

2. MATHEMATICAL MODEL

The subject of analysis is a change in the activity of plasma renin activity after treatment with nicardipine in experimental animals [3,6]. The mathematical model of the process in function of the drug dose is presented in [7]. The dose-dependent model of the regulation kinetics in the state space is:

$$\left\| \begin{matrix} \dfrac{dx_1(t,d)}{dt} \\ \dfrac{dx_2(t,d)}{dt} \end{matrix} \right\| = \left\| \begin{matrix} 0 & 1 \\ -\omega_0^2 & -2.\zeta(d).\omega_0 \end{matrix} \right\| . \left\| \begin{matrix} x_1(t,d)-x_{O1} \\ x_2(t,d)-x_{O2} \end{matrix} \right\| + \left\| \begin{matrix} 0 \\ -K_0(d) \end{matrix} \right\| \tag{1}$$

The initial conditions are:

$x_{01} = 7.58$
$x_{02} = 0$

where: $x_1(t,d), x_2(t,d)$ - the state of the system ;
d - the applied dose [mg/kg];
$\zeta(d) = 4 - e^{-\frac{d+73,9}{123,4}}$ – the damping ratio;
$\omega_0 = 0,64$ - the natural frequency of the process;
$K_0(d) = 3,64.\ln(d) - 14,47$ – the base level

3. STABILITY ANALYSIS

The stability of the system is determined by the state space matrix ***A***:

$$A = \left\| \begin{matrix} 0 & 1 \\ -\omega_0^2 & -2.\zeta(d).\omega_0 \end{matrix} \right\| \tag{2}$$

From the characteristic equation:

$$\det(A - \lambda.I) = \left\| \begin{matrix} -\lambda & 1 \\ -\omega_0^2 & -2.\zeta(d).\omega_0 - \lambda \end{matrix} \right\| \tag{3}$$

the eigenvalues of λ are determined. The solutions are:

$$\lambda_{1,2} = -\zeta(d).\omega_0 \pm \omega_0.\sqrt{\zeta^2(d) - 1} \tag{4}$$

The eigenvalues depend on the applied dose ***d*** by the damping ratio ***ζ.*** Substituting ***ζ*** by its equivalent expression yields:

$$\lambda_{1,2} = -\left(4 - e^{-\frac{d+73,9}{123,4}}\right).\omega_0 \pm \omega_0.\sqrt{3 - e^{-\frac{d+73,9}{123,4}}} = r(d) \pm i.m(d) \tag{5}$$

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Real part:

$$r(d) = -\left(4 - e^{-\frac{d+73,9}{123,4}}\right) \quad (6)$$

Potentially imaginary part:

$$m(d) = \sqrt{3 - e^{-\frac{d+73,9}{123,4}}}$$

3.1. Appreciation of the discriminant

The presence of an imaginary ingredient in the root determines the occurrence of oscillations in the process. The discriminant is:

$$D(d) = 3 - e^{-\frac{d+73.9}{123.4}} \quad (7)$$

The graphical dependence of the discriminant on the dose is in Figure 1. In order to be negative, the dose ***d*** must fulfill the inequality:

$$d < 123{,}43.\ln\left(\frac{1}{3}\right) - 73.9 = -209{,}469 \quad (8)$$

Presumably, the dose is a positive number, and therefore the discriminant is always positive, which precludes obtaining complex solutions regardless of the dose.

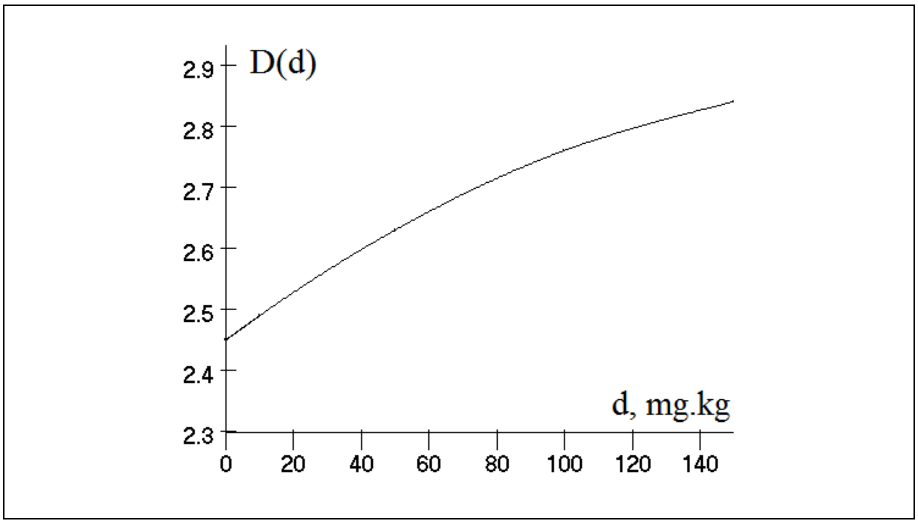

Figure 1.
Dependence of the discriminant on the administered dose

3.2. Appreciation of the real roots

The absence of an imaginary part in the solutions determines the following two real values:

$$\left|\begin{array}{l}\lambda_1=-\left(4-e^{-\frac{d+73,9}{123,4}}\right).0,64+0,64.\sqrt{3-e^{-\frac{d+73,9}{123,4}}}\\ \lambda_2=-\left(4-e^{-\frac{d+73,9}{123,4}}\right).0,64-0,64.\sqrt{3-e^{-\frac{d+73,9}{123,4}}}\end{array}\right. \quad (9)$$

Figure 2 shows their variation in dose function.

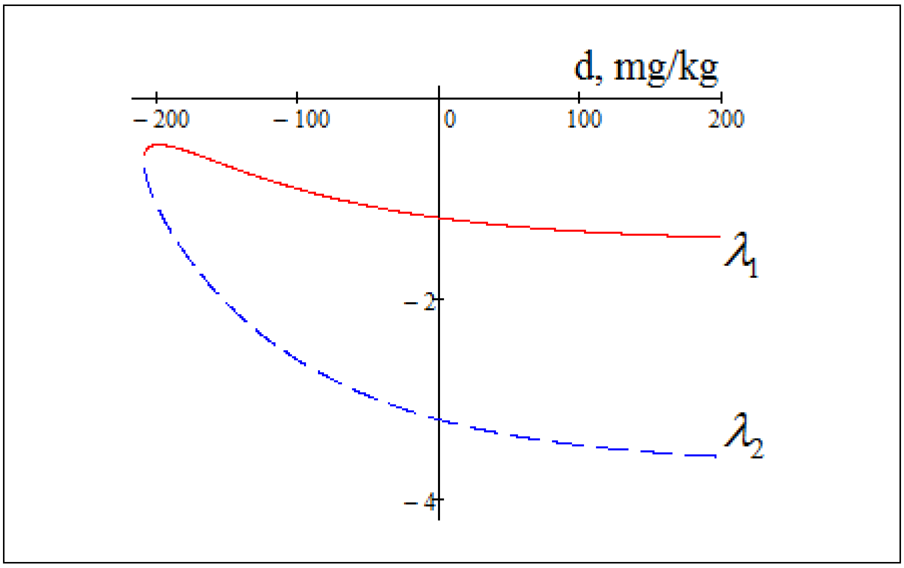

Figure 2.
Dependence of the eigenvalues on the administered dose

The limit to an infinitely large dose again leads to negative values:

$$\left|\begin{array}{l}\lim\limits_{d\to\infty}(\lambda_1(d))=\text{-}1.45\\ \lim\limits_{d\to\infty}(\lambda_2(d))=\text{-}3.67\end{array}\right. \quad (10)$$

The results show that the process is stable regardless of the dose administered. The conclusion obtained by the phase plane method [11] is confirmed.

4. CONCLUSION

In the present work, the stability of the renin-angiotensin system to different doses of nicardipine was investigated. The analysis is made on the mathematical model of PRA change, which is an indicator of PAC behavior. Using bifurcation analysis, critical doses that

would influence the sustainable behavior of PAC are sought. Analytical expressions and graphs show that such points do not exist.
The final conclusion of the study is that administration of nicardipine at random doses cannot induce instability reactions on the system.

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