ARTTE Applied Researches in Technics, Technologies and Education
Journal of the Faculty of Technics and Technologies, Trakia University
https://sites.google.com/a/trakia-uni.bg/artte/

BEHAVIOR OF THE PHARMACOKINETICS OF ENROFLOXACIN IN THE PHASE SPACE

Miroslav Vasilev, Galya Shivacheva
Faculty of Technics and Technologies, Trakia University
38 Graf Ignatiev str., 8602, Yambol, Bulgaria
e-mail: miroslav.vasilev@trakia-uni.bg

Abstract: *Phase space is an approach for analysis of nonlinear differential equations. The graphical solutions that are obtained are convenient for qualitative assessment of the behavior of systems and processes. A comparative analysis of the pharmacokinetics of the antibiotic enrofloxacin administered intravenously in dogs and cats has been performed in the present study. The mathematical models that represent the change in blood plasma concentration of the two groups of animals are described by second-order differential equations. For the graphical representation of phase trajectories using the fluoroquinolone, the Mathcad program tools are used. The properties of the peculiar points are determined based on the received images.*
Keywords: *phase plane, mathematical models, differential equations, Mathcad, pharmacokinetics.*

1. INTRODUCTION

The phase space is an approach for the analysis of linear and nonlinear differential equations. The graphoanalytical solutions offered by the method are convenient for qualitative assessment of the behavior of systems and processes.
Any system, regardless of the order of the differential equation describing it, can be expressed in a multidimensional space, its state being given by the position of its depicting point. It serves as a qualitative characteristic of the transients in the systems.
Although the geometric interpretation of the state space method extends to systems of any order, its important advantage - visibility - is most pronounced in the case of second-order systems when the states of the system are represented by points in the phase plane. It should be added that nonlinear second-order models allow many basic characteristics of the behavior of dynamic systems to be revealed; this determines the methodological, theoretical and practical significance of the phase plane method.
The purpose of this study is to perform a comparative analysis of the pharmacokinetics of the enrofloxacin preparation in blood plasma in cats and dogs using the phase-plane method.

2. MATERIAL AND METHODS

The experimental design and data acquisition methodology are presented in [1]. Identification used their mean and standard deviation.

2.1. Software used

Data processing and analysis are carried out using the specialized software from the KORELIA family. The user-oriented interface and the process recognition module [5] facilitate data entry and support the selection of a mathematical model. The identified equations [8] can be analyzed and compared over a number of parameters [4] and thus found to be the most appropriate for the particular set [7].
Phase-plane analysis was performed with Mathcad. The vector function Rkadapt was solve

ARTTE Applied Researches in Technics, Technologies and Education
Journal of the Faculty of Technics and Technologies, Trakia University
https://sites.google.com/a/trakia-uni.bg/artte/

ordinary differential equations using the fourth order Runge - Kutta method with adaptive step. The eigenvals function was used to calculate the eigenvalues of the state matrix.

2.2. Second-order mathematical model

The mathematical models of the process for the animals studied are presented in [2, 3]. A second-order differential equation is selected for process identification:

$$\begin{cases} \frac{d^2y(t)}{dt^2} + 2.\zeta.\omega.\frac{dy(t)}{dt} + \omega^2 y = K.\omega^2.U(t) \\ y(0) = C_0 \\ \frac{dy(0)}{dt} = 0 \end{cases} \quad \text{initial conditions} \qquad (1)$$

where: U(t) - a dose of enrofloxacin.

Identification parameters are:

ζ – damping ratio;
ω – natural frequency;
K – coefficient of sensitivity.

3. RESULTS

The calculation of the identification parameters for the two species was performed with the KORELIA-Ident program and the values obtained are presented in Table 1.

Table 1. Parameters of the model for the two species

parameter		animals	
in the equation	Mathcad	dogs	cats
ζ	z	6.00	6.83
ω	w	3.40	6.86
K	K	-0.09	-0.12

Figure 1 presents a second-order differential model of the process.

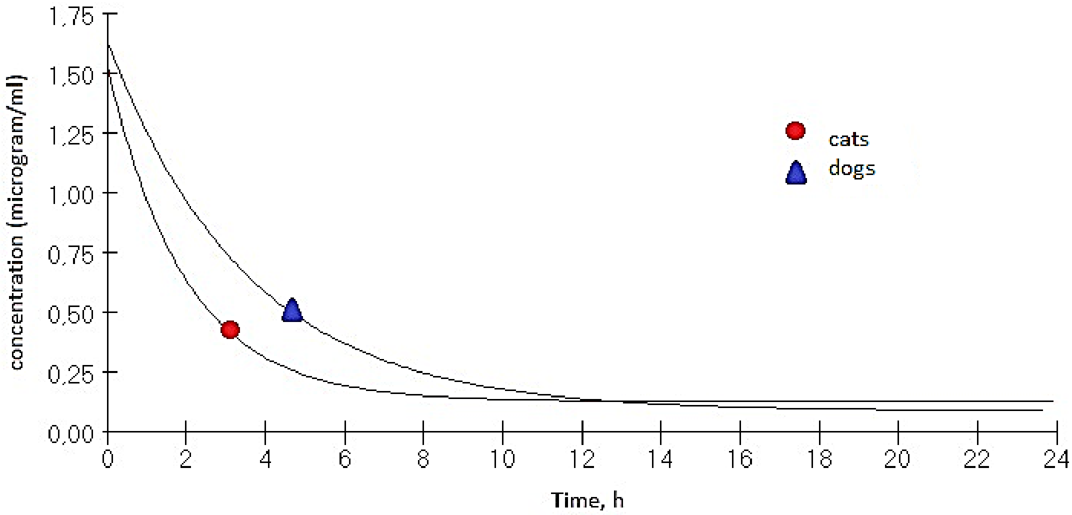

Figure 1. Change in enrofloxacin concentration in dogs and cats

The parameters presented in Table 1 were used to compare the processes of change in the concentration of enrofloxacin in blood plasma in dogs and cats after a single intravenous injection of the substance, using an algorithm for phase-plane analysis [6].

3.1. Model in the Mathcad environment

With the following application:

$$y_1 = y(t)$$

$$y_2 = \frac{dy_1(t)}{dt} \quad (2)$$

Equation (1) is reduced to a system of two first-order differential equations:

$$\left\| \begin{matrix} \frac{dy_1}{dt} \\ \frac{dy_2}{dt} \end{matrix} \right\| = \left\| \begin{matrix} 0 & 1 \\ -\omega^2 & -2\zeta.\omega \end{matrix} \right\| \cdot \left\| \begin{matrix} y_1 \\ y_2 \end{matrix} \right\| \quad (3)$$

The initial conditions are specified in a matrix:

For cats $\rightarrow$ $Y_0 = \begin{pmatrix} 1.53 \\ 0 \end{pmatrix}$

For dogs $\rightarrow$ $Y_0 = \begin{pmatrix} 1.63 \\ 0 \end{pmatrix}$

Other initial values required for modelling are:

t_0=0	// starting point
t_1=24	// the final moment
N1=2000	// number of points in the interval

The vector function required for the ordinary differential equation program is:

$$D(t,Y) = \begin{pmatrix} Y_1 \\ -w^2.Y_0 - 2.z.w.Y_1 \end{pmatrix} \quad (4)$$

The numerical solution is with the operator:

S:=Rkadapt(Y_0, t_0, t_1, N_1, D)

3.2. Phase plane

The space state variables y_1 and y_2 determine the phase plane. In this plane the abscissa is y_1 and the ordinate is y_2 (Figure 2).

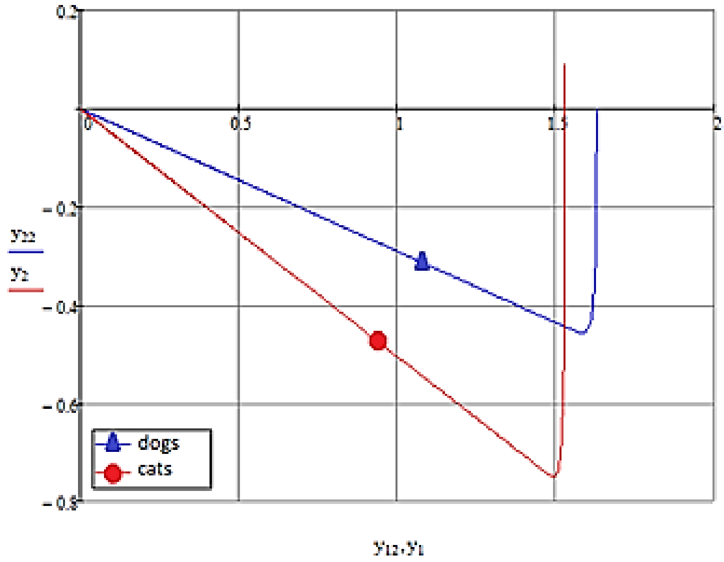

Figure 2. Phase trajectories

3.3. Nullclines of the process

The nullclines of the process are constructed in the coordinate system y_1Oy_2. From the system

$$\begin{Vmatrix} 0 & 1 \\ -\omega^2 & -2\zeta.\omega \end{Vmatrix} \cdot \begin{Vmatrix} y_1 \\ y_2 \end{Vmatrix} = 0 \tag{5}$$

$$\mathrm{M} := \mathrm{A} * \mathrm{Y} + \mathrm{B} \rightarrow \begin{Vmatrix} y_2 \\ -\omega^2 - 2\zeta.\omega \end{Vmatrix} = 0 \tag{6}$$

two solutions are obtained with respect to y_2:

$$M_0 solve, y_2 \rightarrow 0$$

$$M_1 solve, y_2 \rightarrow -\frac{w}{2.z} . y_1$$

The first solution determines the nuclline coinciding with the abscissa. The second solution specifies a nuclline that represents a line passing through the origin of the coordinate system and crossing a nucleon at the singular point.

The last dependence gives the coordinate y_1 for the different species of animals:

$$-\frac{w}{2.z} . y_1 solve, y_1 \rightarrow 0$$

Slope is a measure of the steepness of a straight line. The larger (in absolute value) the steeper the slope. In the model under consideration, its value is calculated by the formula:

$$a = -\frac{w}{2z} \tag{7}$$

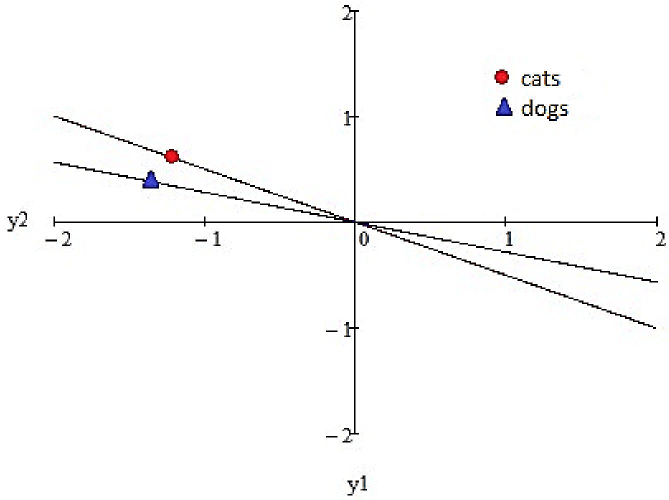

Figure 3. Nullclines of the process

There is one special point. It is obtained as the intersection of the two nullclines and for the studied process in both animal species it is the same and has coordinates (0, 0).

3.4. Eigenvalues of the state matrix

In this case, the eigenvalues of the status matrix for dogs and cats are different. These are derived from the eigenvals function and are generally as follows:

$$ev(w,z) := eigenvals\big(A(w,z)\big) \rightarrow \begin{bmatrix} -w.z - w.\sqrt{z^2-1} \\ -w.z + w.\sqrt{z^2-1} \end{bmatrix} \qquad (8)$$

In the model considered, for both animals the real parts are negative and z>1, which means that the singular points are of the type of stable node - in this case the point with coordinates (0,0). This is evidence of a sustainable process for dogs and cats.

4. DISCUSSION

The values of the identification parameters presented in Table 1 reflect the differences in the process of the two species.
In dogs, the inhibition coefficient is smaller, which means a faster decrease in concentration.
In cats, the intrinsic frequency is higher, which necessitates the administration of the drug at shorter intervals.
The process in cats is characterized by a lower sensitivity coefficient, which means less sensitivity to the preparation and therefore higher doses are recommended.
The inhibition coefficient in both species of animals is greater than one and therefore no oscillatory process is possible, therefore their organisms are not likely to react with a cyclic change in reaction.
In cats the process is characterized by an angular coefficient of -0.50, and in dogs of -0.28. In absolute terms, the higher the ratio in cats. On the graph, the rights that define it are steeper, which is a sign of a higher speed of process in this species of animal. This means that the drug is retained in their body for a shorter time and therefore should be taken at smaller intervals.

A higher suppression coefficient is compensated by a higher natural frequency and is reflected in a higher rate of change of concentration (Figure 3).

5. CONCLUSION

1. Comparative analysis of the pharmacokinetics of enrofloxacin in blood plasma in cats and dogs was performed after a single intravenous injection by the phase-plane method, the change in concentration being described in the space of states. Phase trajectories are constructed. Nullclines of the process were obtained analytically and graphically. The singular points are also determined from the eigenvalues of the state matrix of their type - stable node.
2. The enrofloxacin degrades more rapidly in the body of cats, which necessitates the administration of the drug at smaller intervals. Due to the lower sensitivity, higher doses are recommended.

6. ACKNOWLEDGEMENTS

This study was supported by the Scientific Project: 2.FTT/ 31.03.2017 „Investigation of systems and processes by the phase plane method" of the Faculty of Technics and Technologies of Yambol, Trakia University of Stara Zagora, Bulgaria.
The authors express their deep gratitude to Prof. Dimitrichka Dimitrova, University of Forestry, Sofia, Bulgaria for the provided data, without which this work would not have been possible.

7. REFERENCES

[1] Dimitrova D. (2013). Comparative study of the pharmacokinetics of enrofloxacin in dogs and cats. Pharmacokinetics of some antimicrobial chemotherapeutics in veterinary medicine, Literary Print, Stara Zagora, pp. 93-101. (in Bulgarian).
[2] Shivacheva G., M. Vasilev. (2019). Selection of the mathematical model for the use of enrofloxacin in cats. International Conference on Technics, Technologies and Education ICTTE 2019 October 16-18 2019, Yambol.
[3] Vasilev M., G. Shivacheva. (2019). Comparison of Mathematical Models for the Use of Enrofloxacin in Dogs. ARTTE Vol. 7, No. 2, pp. 97-102.
[4] Yankov K. (2015). Assessment of Processes Using Identification Models. Applied Researches in Technics, Technologies and Education ARTTE, Vol. 3, No. 1, 2015, pp.52-60. doi: 10.15547/artte.2015.01.006.
[5] Yankov K. (2010). Decision Planning of System Identification. Proc. of the Int. Conference on Information Technologies (InfoTech-2010). St. St. Constantine and Elena resort, Sept.16-18, 2010, Varna, Bulgaria, pp. 229-238. ISSN 1314-1023.
[6] Yankov K. (2018). Phase Portrait of Second-Order Dynamic Systems. Applied Researches in Technics, Technologies and Education ARTTE, Vol.6, No. 3, pp. 252-262. doi: 10.15547/artte.2018.03.007.
[7] Yankov K. (2015). Selection of the Approximating Function for Isobologram Modeling. Proc. Int. Conference on Information Technologies (InfoTech-2015). St. St. Constantine and Elena resort, Varna, Bulgaria, Sept. 17-19, 2015. pp. 174-183. ISSN 1314-1023.
[8] Yankov K. (2006). System Identification of Biological Processes. Proc. 20-th Int.Conf. "Systems for Automation of Engineering and Research (SAER-2006). St. St. Constantine and Elena resort, Sept. 23-24, 2006, Varna, Bulgaria, pp. 144-149. ISBN 954-438-575-4.