SELECTION OF THE MATHEMATICAL MODEL FOR THE USE OF ENROFLOXACIN IN CATS

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Abstract: *The process of changing the concentration of enrofloxacin in blood plasma in cats after single intravenous injection was identified by three mathematical models - algebraic and two models represented respectively by a first order differential equation and a second order differential equation. In order to select the best model of the three, the Akaike information criterion corrected is used. With the most identification parameters differs the model based on a second-order differential equation. The lowest value of the Akaike information criterion corrected was also obtained with it. This fact gives reason to choose it for the best model for describing the research process.*

Keywords: *mathematical model, identification, enrofloxacin, Akaike's information criterion, Korelia.*

1. INTRODUCTION

Enrofloxacin is a broad-spectrum antibacterial drug officially registered and authorized for use in veterinary medicine. It belongs to the so-called "second generation" of fluorinated quinolones [2,3]. In [7], the change in the concentration of enrofloxacin in the blood plasma of cats was monitored by comparing the dynamic parameters of the drug's pharmacokinetics with three methods of administration. For each of the routes of treatment: single intravenous and subcutaneous injection of a substance of enrofloxacin hydrochloride and internal tablet administration, algebraic equations are drawn up. They are solutions of first-order differential equations.

The purpose of this study is to select a mathematical model to describe the process of changing the concentration of enrofloxacin in blood plasma in cats after a single intravenous injection. To realize it, identification was made using three mathematical models - algebraic [7], first-order differential and second-order differential. The choice was made using the corrected Akaike information criterion and the number of identification parameters was analyzed.

2. MATERIAL AND METHODS

The experimental design and data acquisition methodology are presented in [3]. 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 [9] and the process recognition module [10,11] facilitate data entry and support the selection of a mathematical model. The identified equations [13] can be analyzed and compared over a number of parameters [8] and thus found to be the most appropriate for the particular set [12].

The quadratic error minimization criterion is applied for optimization. The coefficient of determination R^2 was used to estimate the proximity of the identified parameters to the experimental data for each model.

Due to the existence of three models described with different equations, it is not permissible for their closeness to the data to be estimated by the coefficient of determination. Akaike information criterion (AIC) is suitable for this case [1,5,12].

When the number of information points N is small compared to the number of identification parameters K ($\frac{N}{K} < 40$), it is necessary to use the corrected version of the Akaike information criterion corrected, AICc [4,6]. If $N \rightarrow \infty$ the values of the two criteria converge.

In cases where the AICc results are very similar, additional model evaluation criteria have to be used. Probability of the model ($P_{I,J}$) can be calculated from AICc.

$$P_{I,J} = \frac{1}{1 + e^{0.5\Delta_{I,J}}} \quad (1)$$

where: $\Delta_{I,J} = AICc_I - AICc_J$

I, J – numbers of compared models

For the purpose of comparison, the proof coefficient (Evidence ratio - $ER_{I,J}$), which is the ratio of the reliability of two compared models in the form:

$$ER_{I,J} = \frac{P_{I,J}}{P_{J,I}} = e^{-0.5\Delta_{I,J}} \quad (2)$$

2.2. Mathematical models

Three mathematical models have been identified.

2.2.1. Algebraic Model (Model 1)

In [2] describes in detail the algebraic model used, which is a solution of a first-order differential equation.

$$\left| \begin{array}{l} y(t) = (C_0 - C_\infty)e^{-r \cdot t} + C_\infty \\ C_\infty = \lim_{t \rightarrow \infty} y(t) = \frac{K \cdot U}{r} \end{array} \right. \quad (3)$$

where: $U(t)$ – a dose of enrofloxacin
 C_0 – initial value

Identification parameters are:

r – the rate constant of the process;
 K – coefficient of sensitivity.

2.2.2. Differential first-order model (Model 2)

$$\left| \begin{array}{l} \frac{dy(t)}{dt} + r \cdot y(t) = K \cdot U(t) \\ y(0) = C_0 - \text{initial value} \end{array} \right. \quad (4)$$

where: $U(t)$ – a dose of enrofloxacin

Identification parameters are:

r – the rate constant of the process;
 K – coefficient of sensitivity.

2.2.3. Second-order differential model (Model 3)

It is represented by the equation:

$$\left| \begin{array}{l} \frac{d^2y(t)}{dt^2} + 2 \cdot \zeta \cdot \omega \cdot \frac{dy(t)}{dt} + \omega^2 y = K \cdot \omega^2 \cdot U(t) \\ y(0) = C_0 \\ \frac{dy(0)}{dt} = 0 \end{array} \right. \quad \begin{array}{l} \\ \text{initial conditions} \end{array} \quad (5)$$

where: $U(t)$ – a dose of enrofloxacin

Identification parameters are:

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

3. RESULTS AND DISCUSSION

The identification parameters for each of the three models were calculated using the KORELIA-Ident program. The following equations are derived from them:

$$\text{Model 1} \quad y(t) = 1.34 \cdot e^{-0.42t} + 0.10 \quad (6)$$

$$\text{Model 2} \quad \frac{dy(t)}{dt} - 0.39 \cdot y(t) = 0 \quad (7)$$

$$\text{Model 3} \quad \frac{d^2y(t)}{dt^2} + 93.71 \frac{dy(t)}{dt} + 47.06y = -28.24 \quad (8)$$

Figure 1 shows the graphs of the models.

Figure 1.
Change in enrofloxacin concentration in the three models

The parameters used to compare the three mathematical models are presented in Table 1. To calculate the reliability of the model and the coefficient of proof are formulas (1) and (2) used. The calculations are done with Excel. The values for R^2 , quadratic error and AICc were obtained by identifying with the KORELIAIdent program. A corrected version of AIC was used to select a model from all three reasons the relatively similar values of N and K in the process studied.

Table 1. Comparison of models after identification

Model	Number of identification parameters	R^2	Quadratic error	AICc	$\Delta AICc$	$P_{I,J}$	$ER_{I,J}$
Model 3	3	0,980	0,045	-2304			
Model 1	2	0,987	0,030	-2192	112	6,7917E-25	1,47239E+24
Model 2	2	0,964	0,082	-2151	153	5,53578E-34	1,80643E+33

The best model according to the AICc criterion is the one with the smallest value. The fulfillment of this condition is the second-order differential model - Model 3. The values of $P_{I,J}$ and $ER_{I,J}$ show that the three models differ from each other.

4. CONCLUSION

The process of change in the concentration of the drug enrofloxacin in the blood plasma of cats after a single intravenous injection was identified by three mathematical models - algebraic, first-order differential and second-order differential. The corrected Akayke information criterion was used to select the "optimal" model. Its lowest value is obtained in a mathematical model based on a second order differential equation and different from the other two with more identification parameters - three in number.

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