CONFERENCE PROCEEDINGS

17-19 October 2018, Almaty, Kazakhstan

www.aict.info/2018

CONFERENCE PROCEEDINGS

2018 IEEE 12th International Conference on Application of Information and Communication Technologies (AICT)

IEEE Catalog Number: CFP1856H-PRT
ISBN: 978-1-5386-6467-4

Additional copies of this publication are available from
Curran Associates, Inc.
57 Morehouse Lane
Red Hook, NY 12571 USA
+1 845 758 0400
+1 845 758 2633 (FAX)
email: curran@proceedings.com

IEEE Catalog Number: CFP1856H-PRT
ISBN: 978-1-5386-6467-4

Solving the Reverse Problems of Pharmacokinetics for a Linear Two-Compartment Model with Absorption

Baydaulet A. Urmashev, Aisulu T. Tursynbay, Almas N.Temirbekov, Aidana B. Amantayeva
Kazakh National University named after al-Farabi, Almaty, Kazakhstan
baydaulet.urmashev@kaznu.kz, tursynbay_a@mail.ru, almas.temirbekov@kaznu.kz, aman.aydana@gmail.com

***Abstract* — A new method is proposed for revealing the nonuniqueness of the solution of the inverse problem. The existence of three solutions of this equation is analytically proved and an algorithm for their finding is presented. The obtained results indicate the ambiguity of solutions of inverse problems and the obtained sets of parameters of the corresponding numerical methods for solving inverse problems of pharmacokinetics require additional conditions for determining the necessary set of pharmacokinetic parameters.**

Keywords — Pharmacokinetics; nonuniqueness of the solution inverse problems; numerical methods; linear two-compartment model with absorption;

I. INTRODUCTION

The theoretical proof of the nonuniqueness of the solution is confirmed by numerical calculations. To solve the inverse problem of models of pharmacokinetics, there were used several numerical methods that satisfy the criterion of the method of least squares. The software complex pharmacokinetics 2.0 was developed. High performance will be provided by developing algorithms to solve the main problems in Fortran and C programming languages. These de-facto programming languages are the fastest for implementation of complex mathematical calculations. The applications developed in these programming languages will be called through the architecture of micro services. Using the example of a computational experiment, the software complex was used for finding the pharmacokinetic parameters for a linear two-chamber pharmacokinetics model with absorption.

II. RELATED WORK

Previously, in the works [1, 2] we studied the kinetics of the reaction system (1), (2). It was shown that the equation of the dependence of concentration on time for component B has more than one solution. The result of this work is a rigorous analytical substantiation of the number of solutions of this equation and the identification of the conditions for the realization of each of them.

The chemical kinetics of processes (1-2) is described by the solution of the Cauchy problem for a system of linear ordinary differential equations (3-10):

$$\underset{C_1}{A} \xrightarrow{k_1} \underset{C_2}{B} \xrightarrow{k_2} \underset{C_3}{C} \tag{1}$$

$$\underset{C_2}{B} \xleftrightarrow{k_{3,4}} \underset{C_4}{D} \tag{2}$$

$$\frac{dC_1}{dt} = -k_1 C_1 \tag{3}$$

$$\frac{dC_2}{dt} = k_1 C_1 - (k_2 C_2 + k_3 C_2) + k_4 C_4 \tag{4}$$

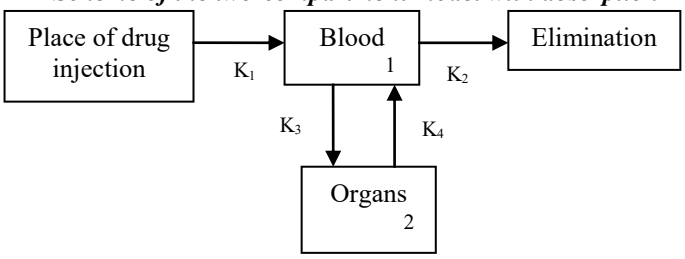
$$\frac{dC_3}{dt} = k_2 C_2 \tag{5}$$

$$\frac{dC_4}{dt} = k_3 C_2 - k_4 C_4 \tag{6}$$

$$C_1(0) = C_0, C_2(0) = 0, C_3(0) = 0, C_4(0) = 0, \tag{7-10}$$

here $C_i(t)$ - concentration of components **A, B, C, D** at the time moment t, k_i - rate constants of the individual reaction stages 1 and 2.

Scheme of the two-compartment model with absorption



On the basis of differential equations (3-6) with the above-mentioned initial conditions, the desired dependence $C_2(t) = f(t)$ - the dynamics of the change in the concentration of component **B** can be represented in the form of equation 11 [3, 4].

$$C_2(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} - A_3 e^{-k_1 t}, \tag{11}$$

where:

$$A_1 = \frac{k_1(\lambda_1 - k_4)\cdot C_0}{(\lambda_1 - \lambda_2)(k_1 - \lambda_1)} \tag{12}$$

$$A_2 = \frac{k_1(\lambda_2 - k_4)C_0}{(\lambda_1 - \lambda_2)(\lambda_2 - k_1)} \tag{13}$$

$$A_3 = -(A_1 + A_2) = \frac{k_1(k_4 - k_1)C_0}{(k_1 - \lambda_1)(k_1 - \lambda_2)} \tag{14}$$

$$\lambda_{1,2} = \frac{1}{2}\cdot\left[(k_2 + k_3 + k_4) \pm \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}\right] \tag{15}$$

$$\lambda_1 + \lambda_2 = k_2 + k_3 + k_4,\ \lambda_1\lambda_2 = k_2k_4 \tag{16-17}$$

The solution of the direct problem in this case is not difficult. In Fig.1 presented calculated values of the concentration of substance **B** for the given values of reaction rate constants k_i and its initial concentration equal to 50.

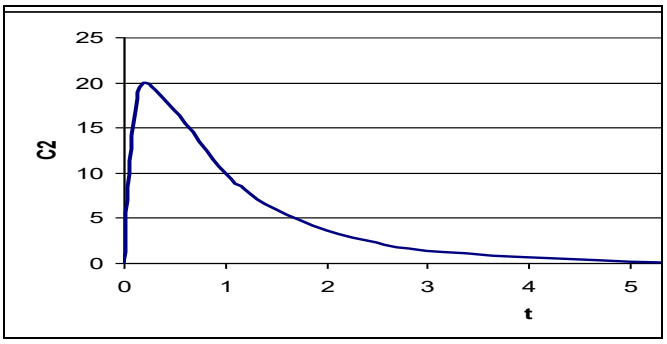


Fig. 1. Dependencies of concentration $C_2(t)$ on time for values.

$$C_0 = 50, k_1 = 5, k_2 = 2, k_3 = 3, k_4 = 4 \cdot$$

III. MATERIALS AND METHODS

The inverse problem is the calculation of the quantities k_i and C_0 on the basis of some set of measured values C_{2i} at the time moment t_i, in comparison to the straight one, is a much more complicated problem [4]. To solve it, equation (11) is presented in the following form (18):

$$C_2^{calc}(t) = L_1 e^{-\varepsilon_1 t} + L_2 e^{-\varepsilon_2 t} + L_3 e^{-\varepsilon_3 t} \quad (18)$$

Coefficients L_i and ε_i of this equation are related as follows:

$$L_1 + L_2 + L_3 = 0, \quad (19)$$

$$\varepsilon_1 \neq \varepsilon_2 \neq \varepsilon_3, \quad (20)$$

$$\varepsilon_1 > 0, \varepsilon_2 > 0, \varepsilon_3 > 0. \quad (21)$$

Taking into account equality (19), the total number of unknowns in equation (18) decreases until 5. Values of $L_1, L_2, \varepsilon_1, \varepsilon_2, \varepsilon_3$ were found by the method of least squares:

$$\sum_i \left(C_2^{\exp}(t_i) - C_2^{calc}(t_i)\right)^2 \to \min$$

where $C_2^{\exp}(t_i)$ - the concentrations found experimentally, $C_2^{calc}(t_i)$ - their calculated values.

After determining the values L_i and ε_i several options for assigning values $\varepsilon_1 \neq \varepsilon_2 \neq \varepsilon_3$ for $\lambda_1, \lambda_2, k_1$ were considered. Taking into account the conjugacy of the roots λ_1 and λ_2 ($\lambda_1 > \lambda_2$), and sampling two of three $\varepsilon_1, \varepsilon_2, \varepsilon_3$ possible, we can obtain the following cases:

1) $\lambda_1 = \varepsilon_1$, $\lambda_2 = \varepsilon_2$, $k_1 = \varepsilon_3$, (22)

2) $\lambda_1 = \varepsilon_2$, $\lambda_2 = \varepsilon_3$, $k_1 = \varepsilon_1$, (23)

3) $\lambda_1 = \varepsilon_1$, $\lambda_2 = \varepsilon_3$, $k_1 = \varepsilon_2$, (24)

Further, using equations (12-14) to calculate the coefficients A_i, we obtain the systems of equations (12_1-14_1), (12_2-14_2) and (12_3-14_3) for calculating L_1^i, L_2^i, L_3^i, $i = \overline{1..3}$ respectively:

$$L_1^i = \frac{\varepsilon_3(\varepsilon_1 - k_4)\cdot C_0^1}{(\varepsilon_3 - \varepsilon_1)(\varepsilon_1 - \varepsilon_2)} \quad (12_i)$$

$$L_2^i = \frac{\varepsilon_3(k_4 - \varepsilon_2)\cdot C_0^1}{(\varepsilon_3 - \varepsilon_2)(\varepsilon_1 - \varepsilon_2)} \quad (13_i)$$

$$L_3^i = \frac{\varepsilon_3(\varepsilon_3 - k_4)\cdot C_0^1}{(\varepsilon_3 - \varepsilon_1)(\varepsilon_3 - \varepsilon_2)} \quad (14_i)$$

Since for constants L_i there are only values L_1, L_2, L_3, then the above systems of equations can be reduced to the following:

$$L_1^1 = L_3^2 = L_1^3 = L_1 \quad (25_1)$$

$$L_2^1 = L_1^2 = L_3^3 = L_2 \quad (25_2)$$

$$L_3^1 = L_2^2 = L_2^3 = L_3 \quad (25_3)$$

It follows that the initial concentrations for the three variants are related to each other by equality:

$$C_0^1 \varepsilon_3 = C_0^2 \varepsilon_1 = C_0^3 \varepsilon_2 \quad (26)$$

From the equation for calculating the rate constants k_4 (27), it is clear that in the realization of any of the three variants (22-24), its magnitude remains constant:

$$k_4 = -\frac{L_1\varepsilon_2\varepsilon_3 + L_2\varepsilon_1\varepsilon_3 + L_3\varepsilon_1\varepsilon_2}{L_1\varepsilon_1 + L_2\varepsilon_2 + L_3\varepsilon_3} \quad (27)$$

This leads to a very important conclusion in a practical sense: k_4 can serve as the main criterion for the selection of well-founded solutions describing the investigating set of points $C_2 - t$ for measured solution. To justify this conclusion, let us return to equations (16-17):

For $k_3 > 0$ we obtain the following inequality:

$$\lambda_1 + \lambda_2 > k_2 + k_4. \quad (28)$$

Then, from the equation (17) we can find k_2:

$$k_2 = \lambda_1\lambda_2 / k_4 \quad (29)$$

and substituting it in (28), we obtain a new inequality of the form:

$$k_4^2 - (\lambda_1 + \lambda_2)k_4 + \lambda_1\lambda_2 < 0. \quad (30)$$

The solution of the last inequality can be represented in this form:

$$k_4 \in (\lambda_2, \lambda_1). \quad (31)$$

This means that the reaction rate constant (2) $k_3 > 0$ will be positive only if the computed value k_4 will be between the roots λ_1 and λ_2.

Otherwise, it will take a negative value. It should be noted that inequality (28) also holds in this case. For the computed values ε_i, connected by inequality (20), we find their

maximum - $\varepsilon_{\max}$ and minimum - $\varepsilon_{\min}$ meanings. Now, one of the three values ε_i ($\bar{\varepsilon}$) belongs to the segment:

$$\bar{\varepsilon} \in (\varepsilon_{\min}, \varepsilon_{\max}).$$

From this it is not difficult to see that for k_4 two variants can be realized:

$$k_4 \in (\varepsilon_{\min}, \bar{\varepsilon}) \text{ and } k_4 \in (\bar{\varepsilon}, \varepsilon_{\max}).$$

Thus, the total number of solutions for equation (18) can be equal to three. Proof of the fact that the dependence $C_2(t) = f(t)$ can be simultaneously described by three sets of values k_i and C_0 S_n functions and Laplace transforms were used.

Originally, S_n denotes definite integrals, called the Laplace transforms:

$$S_n = C_0 \frac{k_1}{k_1 + n} \cdot \frac{n + k_4}{(\lambda_1 + n)(\lambda_2 + n)} \quad (32)$$

Here n - can be any real number, but for convenience there were taken integer values.

Since in the solution of the inverse problem for equation (11) or (18) it is necessary to determine the values of five unknowns, we can confine ourselves to five equations.

$$x_1 + nx_2 + \frac{1}{n^2}\left(1 - \frac{S_0}{S_n}\right)x_3 - \frac{S_0}{n \cdot S_n} x_4 = \frac{1}{n}\xi \quad (33)$$

where

$$x_1 = 1 + (\lambda_1 + \lambda_2)/k_1,\ x_2 = 1/k_1,\ x_3 = \lambda_1\lambda_2, \quad (34)$$
$$x_4 = k_2,\ \xi = -x_2x_3 - (x_1 - 1)/x_2.$$

Then, by introducing new notation:

$$\begin{cases} ax_3 + bx_4 = \frac{1}{3}\xi \\ cx_3 + dx_4 = \frac{3}{4}\xi \end{cases} \quad (35)$$

And solving the system of equations (35) and taking into account that $x_i = B_i\xi$ we define successively all values B_i:

$$B_4 = \frac{\frac{1}{3}c - \frac{3}{4}a}{dc - ad},\ B_3 = \frac{\frac{1}{3}d - \frac{3}{4}b}{ad - bc} \quad (36\text{-}37)$$

$$B_2 = -\frac{1}{2} - \left(\frac{S_0}{S_1} - \frac{S_0}{4S_2} - \frac{3}{4}\right)B_3 - \left(\frac{S_0}{S_1} - \frac{S_0}{2S_2}\right)B_4 \quad (38)$$

$$B_1 = 1 - B_2 - \left(1 - \frac{S_0}{S_1}\right)B_3 + \frac{S_0}{S_1}B_4 \quad (39)$$

Further, substituting $x_i = B_i\xi$ into equation (34) we obtain the cubic equation (40)

$$B_2^2B_3\xi^3 + B_2\xi^2 + B_1\xi - 1 = 0, \quad (40)$$

The roots of which are found using the Cardano formula. The nonlinear equation (40) can be solved by a variety of different numerical methods, we chose the simplest of them - Newton's method. The algorithm for finding three values ξ_i is simple. First, using Newton's method, we determine the value ξ_1, and then using equality:

$$ax^3 + bx^2 + cx + d = (x - \xi)(ax^2 + (b + a\xi)x + a\xi^2 + b\xi + c) \quad (41)$$

and solving the quadratic equation:

$$ax^2 + (b + a\xi)x + a\xi^2 + b\xi + c = 0 \quad (42)$$

We find the remaining two solutions ξ_2 and ξ_3.

Thus, it follows from the above proof that for the measured solutions of $C_2(t)$ and the initial condition $C_2(0) = 0$, There are three sets of five permanent C_0, k_1, k_2, k_3, k_4 for the system (3-10).

1. For each of the variants of dependence $C_2(t) = f(t)$ with specified values of variables k_i and C_0 there are two more sets of these constants, that is, the inverse problem, in contrast to the straight one has three solutions.
2. Despite the fact that the given (measured) data set $C_2 - t$ can be described by three sets of constants k_i and C_0, only two of them have a physical meaning; The third set with a rate constant k_3, which has negative value and no physical meaning.
3. Thus, the inverse problem is the determination of the rate constants k_i and initial concentration C_0 by data $C_2 - t$ is incorrect, since the number of solutions is not equal to one [4]. And if the data set $C_2 - t$ is given by a direct problem, then the inverse problem, being ill-posed, has a stable solution. This is confirmed by the fact that one of the solutions found coincides with a given set of rate constants k_i and C_0.

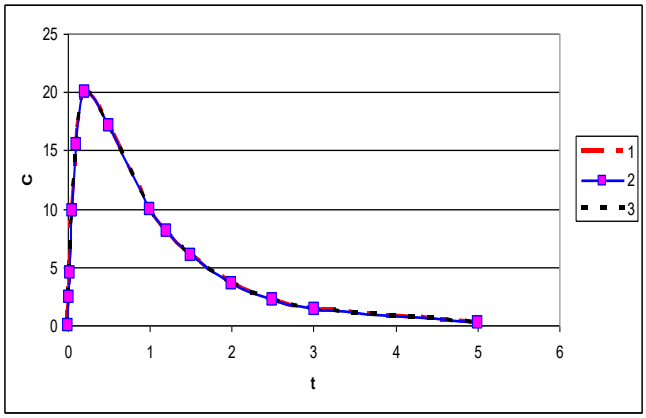


Fig. 2. Dependencies of $C_2(t)$ on time for different values $\xi_{1,2,3}$.

This fact also serves as a criterion for the correctness of the proposed mathematical apparatus and the calculations performed. In addition, the results of the study completely confirm the reliability of the data obtained earlier, where the proof of the non-uniqueness of the solution for the inverse problem was obtained in a different way [1, 2].

During the solution of inverse problem from experimental data, $C_2 - t$ is complicated by the fact that the instability is added to the problem of nonuniqueness of the solution. The problem of incorrectness of the inverse problem, caused by the instability of its solution, is one of the main problems in this field of knowledge. Its severity can be reduced by the continuous improvement of the optimization procedures used and the quality of the experiment. However, completely this problem can not be solved in principle.

IV. RESULTS AND DISCUSSION

To clarify the stability of finding the coefficients of the model of pharmacokinetics, experimental values of the dependence $C_2(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} - A_3 e^{-k_1 t}$ on time for values $C_0 = 50, k_1 = 10, k_2 = 1, k_3 = 5, k_4 = 3$. with a minimum absolute error in 1%.

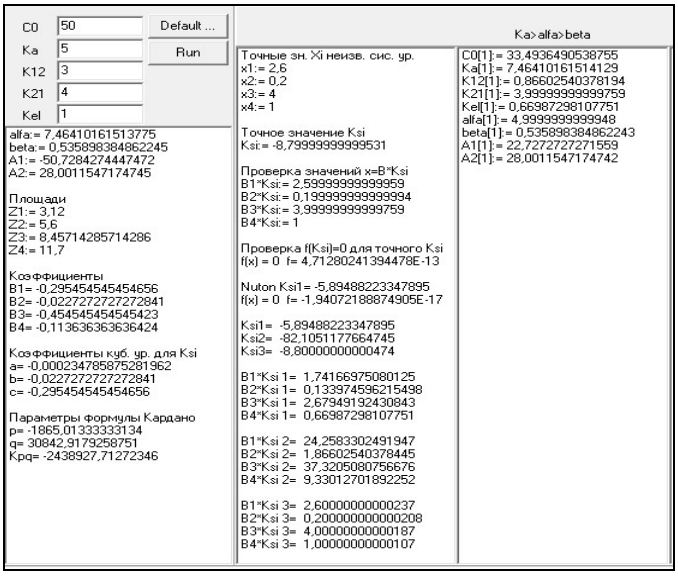


Fig. 3. Results of a numerical experiment, confirming the existence of three solutions for the equations (18) and respectively (11).

Using the proven methods of solving inverse problems, unknown parameters for the given experimental data were found. Unfortunately, the found parameters are very different from the model parameters. We can make sure to see the following figure.

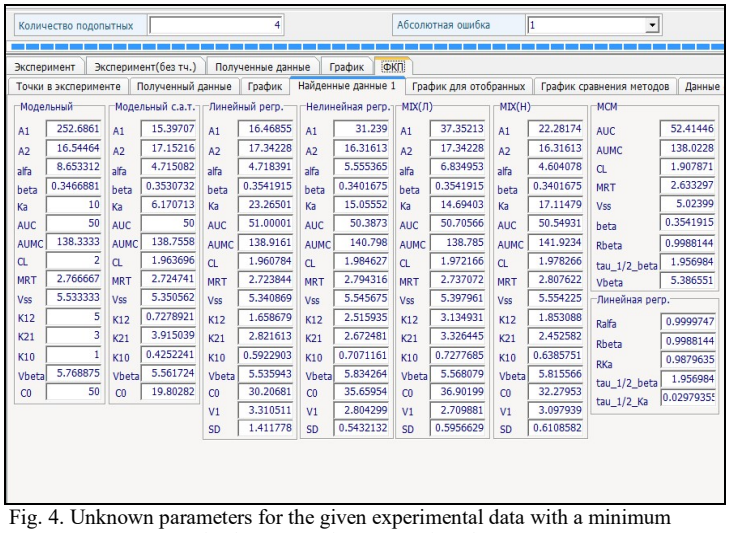


Fig. 4. Unknown parameters for the given experimental data with a minimum absolute error of 1%. were found .

You can also illustrate the graphical data for the parameters found using numerical methods.

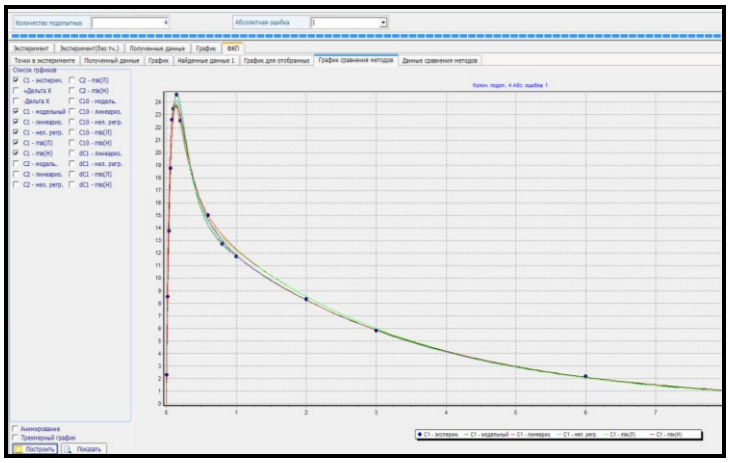


Fig. 5. Graphical dependences of concentration in the central chamber for the data from Fig. 4.

Here we can see a good coincidence for the central chamber of a linear two-chamber pharmacokinetics model with absorption. For the second chamber, the concentration curves are very different from the actual model concentration curve. This can be seen in the Fig. 6.

It can be seen from the figure that the concentration curves of the preparation in the peripheral chamber by quantitative values are almost two times different from the model preset values (red curve).

In the literature, there are many examples of the analysis of pharmacokinetic data [5-8]. A model is constructed for a particular process. Equations describing the corresponding model are given. There used the least squares method (LSM) for determining the parameters involved in the model equations, but often poorly or do not pay attention to the estimated statistical value.

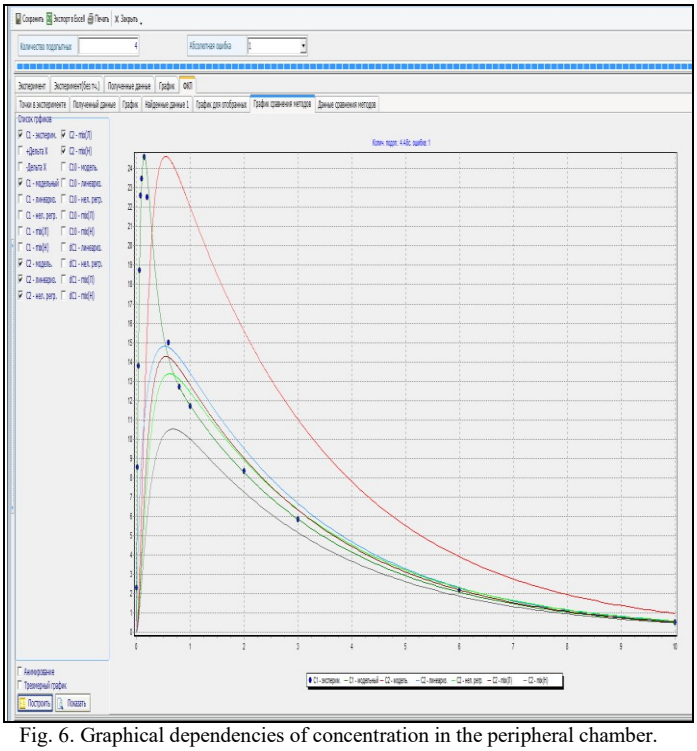


Fig. 6. Graphical dependencies of concentration in the peripheral chamber.

The purpose of this paper presents several important statistical aspects included in the describing equations and finding the values of the pharmacokinetic parameters with the corresponding confidence intervals. The general principle and procedure of the method is proposed in order to obtain statistical parameters.

A two-compartment model of pharmacokinetics with intravascular injection is considered. The change in the concentration of drugs in the blood is described by the equation (54):

$$C(t_i) = A_1 e^{-\alpha t_i} + A_2 e^{-\beta t_i} - (A_1 + A_2) e^{-k_A t_i} \qquad (43)$$

It is well known that the best statistical parameters can be determined using LSM. The present paper deals with the case of drug distribution, which are described by four parameters. When the experimentally found values $C_i^{\exp}$ characterizes by equation $C(t_i, A_1, A_2, \alpha, \beta, k_A)$,parameter $A_1, A_2, \alpha, \beta, k_A$ should give the minimum value of the weighted sum of squared differences between $C_i^{\exp}$ and $C(t_i, A_1, A_2, \alpha, \beta, k_A)$, that is,

$$S = \sum_{i=1}^{N} (C_i^{экс} - C(t_i, A_1, A_2, \alpha, \beta))^2 \cdot \omega_i \to \min \cdot \qquad (44)$$

In our case ω_i=1, N is the number of experimental points. At S→min determines the values $A_1, A_2, \alpha, \beta, k_A$ in equation (54).

When $A_1^o, A_2^o, \alpha^o, \beta^o, k_A^o$ is the solution of inverse problem (54) for given experimental data $C_i^{\exp}$, then $A_1^o, A_2^o, \alpha^o, \beta^o, k_A^o$ accepted as approximate values $A_1, A_2, \alpha, \beta, k_A$ and respectively, the best parameters can be given in the following form

$$A_1 = A_1^0 + \Delta A_1, A_2 = A_2^0 + \Delta A_2, \alpha = \alpha^0 + \Delta\alpha,$$
$$\beta = \beta^0 + \Delta\beta, k_A = \Delta k^0 + \Delta k_A$$

where $\Delta A_1, \Delta A_2, \Delta\alpha, \Delta\beta, \Delta k_A$ are growth for parameters $A_1, A_2, \alpha, \beta, k_A$, respectively.

The dependence $C(t_i, A_1, A_2, \alpha, \beta, k_A)$ is expanded in a Taylor series for $A_1^o, A_2^o, \alpha^o, \beta^o, k_A^o$. Then we determine that

$$\Delta C_i = C_i^{\exp} - C(t_i, A_1, A_2, \alpha, \beta, k_A).$$

Further, using the Taylor series expansion, we obtain the following equations:

$$\Delta C_i = \delta_o^i - \delta_{A_1}^i \Delta A_1 - \delta_{A_2}^i \Delta A_2 - \delta_\alpha^i \Delta\alpha - \delta_\beta^i \Delta\beta - \delta_{k_A}^i \Delta k_A$$

where

$$\delta_0^i = C_i^{\exp} - C(t_i, A_1^0, A_2^0, \alpha^0, \beta^0),$$
$$\delta_{A_1}^i = \frac{\partial C(t_i, A_1^0, A_2^0, \alpha^0, \beta^0)}{\partial A_1},$$
$$\delta_{A_2}^i = \frac{\partial C(t_i, A_1^0, A_2^0, \alpha^0, \beta^0)}{\partial A_2},$$
$$\delta_\alpha^i = \frac{\partial C(t_i, A_1^0, A_2^0, \alpha^0, \beta^0)}{\partial \alpha},$$
$$\delta_\beta^i = \frac{\partial C(t_i, A_1^0, A_2^0, \alpha^0, \beta^0)}{\partial \beta}.$$

Based on the LSM principle, the following system of equations is given for unknown quantities $\Delta A_1, \Delta A_2, \Delta\alpha, \Delta\beta, \Delta k_A$.

$$\begin{cases} (\delta_{A_1}, \delta_{A_1})\Delta A_1 + (\delta_{A_1}, \delta_{A_2})\Delta A_2 + (\delta_{A_1}, \delta_\alpha)\Delta\alpha + (\delta_{A_1}, \delta_\beta)\Delta\beta + (\delta_{A_1}, \delta_{k_A})\Delta k_A = (\delta_{A_1}, \delta_0) \\ (\delta_{A_1}, \delta_{A_2})\Delta A_1 + (\delta_{A_2}, \delta_{A_2})\Delta A_2 + (\delta_\alpha, \delta_{A_2})\Delta\alpha + (\delta_\beta, \delta_{A_2})\Delta\beta + (\delta_{k_A}, \delta_{A_2})\Delta k_A = (\delta_{A_2}, \delta_0) \\ (\delta_{A_1}, \delta_\alpha)\Delta A_1 + (\delta_{A_2}, \delta_\alpha)\Delta A_2 + (\delta_\alpha, \delta_\alpha)\Delta\alpha + (\delta_\beta, \delta_\alpha)\Delta\beta + (\delta_{k_A}, \delta_\alpha)\Delta k_A = (\delta_\alpha, \delta_0) \\ (\delta_{A_1}, \delta_\beta)\Delta A_1 + (\delta_{A_2}, \delta_\beta)\Delta A_2 + (\delta_\alpha, \delta_\beta)\Delta\alpha + (\delta_\beta, \delta_\beta)\Delta\beta + (\delta_{k_A}, \delta_\beta)\Delta k_A = (\delta_\beta, \delta_0) \\ (\delta_{A_1}, \delta_{k_A})\Delta A_1 + (\delta_{A_2}, \delta_{k_A})\Delta A_2 + (\delta_\alpha, \delta_{k_A})\Delta\alpha + (\delta_\beta, \delta_{k_A})\Delta\beta + (\delta_{k_A}, \delta_{k_A})\Delta k_A = (\delta_{k_A}, \delta_0) \end{cases} \qquad (45)$$

where

$$\delta_{A_1} = \{\delta_{A_1}^1, \delta_{A_1}^2, ..., \delta_{A_1}^N\}, \delta_{A_2} = \{\delta_{A_2}^1, \delta_{A_2}^2, ..., \delta_{A_2}^N\}, \delta_\alpha = \{\delta_\alpha^1, \delta_\alpha^2, ..., \delta_\alpha^N\},$$
$$\delta_\beta = \{\delta_\beta^1, \delta_\beta^2, ..., \delta_\beta^N\}, \delta_{k_A} = \{\delta_{k_A}^1, \delta_{k_A}^2, ..., \delta_{k_A}^N\},$$
$$\delta_{A_1}^i = e^{-\alpha^0 t_i} - e^{-k_A^0 t_i}, \delta_{A_2}^i = e^{-\beta^0 t_i} - e^{-k_A^0 t_i}, \delta_\alpha^i = -A_1^0 t_i e^{-\alpha^0 t_i}, \delta_\beta^i = -A_2^0 t_i e^{-\beta^0 t_i},$$
$$\delta_{k_A}^i = (A_1^0 + A_2^0) t_i e^{-k_A^0 t_i}.$$

The best parameters can be obtained by the roots of the above system (56). Solving the system of equations by the numerical

method of Gauss determine the values of the unknowns $\Delta A_1, \Delta A_2, \Delta\alpha, \Delta\beta, \Delta k_A$

The system (56) can be written in the following matrix form

$$\Lambda \cdot \Delta_x = \Delta_0$$

We denote by C the inverse matrix in (45)

$$C = \Lambda^{-1}$$

The solution $\Delta A_1, \Delta A_2, \Delta\alpha, \Delta\beta, \Delta k_A$ of system (45) can be represented in vector form:

$$\Delta_x = \Lambda^{-1} \cdot \Delta_0$$

here

$$\Lambda = \begin{pmatrix} (\delta_{A_1}, \delta_{A_1}) & (\delta_{A_1}, \delta_{A_2}) & \dots & (\delta_{A_1}, \delta_{k_A}) \\ (\delta_{A_1}, \delta_{A_2}) & (\delta_{A_2}, \delta_{A_2}) & \dots & (\delta_{k_A}, \delta_{A_2}) \\ \dots & \dots & \dots & \dots \\ (\delta_{A_1}, \delta_{k_A}) & (\delta_{A_2}, \delta_{k_A}) & \dots & (\delta_{k_A}, \delta_{k_A}) \end{pmatrix}$$

$$\Delta_0 = \left((\delta_{A_1}, \delta_o); (\delta_{A_2}, \delta_o); (\delta_\alpha, \delta_o); (\delta_\beta, \delta_o); (\delta_{k_A}, \delta_o)\right)$$

$$\Delta_x = \left(\Delta A_1 \ \Delta A_2 \ \Delta\alpha \ \Delta\beta \ \Delta k_A\right)^T$$

The statistical values are given by the following equations.

$$S = (\delta_0, \delta_0) - (\delta_{A_1}, \delta_0)\Delta A_1 - (\delta_{A_2}, \delta_0)\Delta A_2 - (\delta_\alpha, \delta_0)\Delta\alpha - (\delta_\beta, \delta_0)\Delta\beta - (\delta_{k_A}, \delta_0)\Delta$$

$\sigma^2 = S/(N-2)$ - sum of squares.

The standard deviation of the parameters of equation (43) $A_1, A_2, \alpha, \beta, k_A$:

$$SD_{A_1} = \sqrt{c_{11}\sigma^2}, SD_\alpha = \sqrt{c_{33}\sigma^2}, SD_\beta = \sqrt{c_{44}\sigma^2},$$

$$SD_{k_A} = \sqrt{c_{55}\sigma^2}.$$

where c_{ii} – elements of the inverse matrix of system of equations (56).

The covariance coefficient can be expressed as the percentage of the coefficient of change $\%CV = \frac{SD}{\theta_i} \times 100$

Where θ_i is one of the parameters $A_1, A_2, \alpha, \beta, k_A$.

Confidence intervals at 95% for each parameter can be given by the following equation:

$CI = SD \times t_{95}$.

By knowing the values $SD_{A_1}, SD_{A_2}, SD_\alpha, SD_\beta, SD_{k_A}$ it needs to be determined $SD_{C_0}, SD_{k_{21}}, SD_{k_{12}}, SD_{k_{10}}$

Let's write the formulas for constants:

$$k_{21} = \frac{\alpha\beta(A_1 + A_2) - A_1 k_A \beta - A_2 k_A \alpha}{A_1\alpha + A_2\beta - (A_1 + A_2)k_A};$$

$$k_{10} = \frac{\alpha\beta}{k_{21}};$$

$$k_{12} = (\alpha + \beta) - k_{21} - k_{10};$$

$$C_0 = \frac{A_2(\alpha - \beta)(k_A - \beta)}{k_A(k_{21} - \beta)};$$

1. $SD_{k_{21}} = k_{21}\sqrt{\left(3\left(\frac{SD_{k_A}^2}{k_A^2} + \frac{SD_\alpha^2}{\alpha^2} + \frac{SD_\beta^2}{\beta^2}\right) + 4\left(\frac{SD_{A_1}^2}{A_1^2} + \frac{SD_{A_2}^2}{A_2^2}\right)\right)}$

2. $SD_{k_{10}} = k_{10}\sqrt{\left(\frac{SD_{k_{21}}^2}{k_{21}^2} + \frac{SD_\alpha^2}{\alpha^2} + \frac{SD_\beta^2}{\beta^2}\right)}$

3. $SD_{k_{12}} = \sqrt{SD_\alpha^2 + SD_\beta^2 + SD_{k_{21}}^2 + SD_{k_{10}}^2}$

4. $SD_{C_0} = C_0\sqrt{4\left(\frac{SD_{A_2}^2}{A_2^2} + \frac{SD_\beta^2}{\beta^2}\right) + 2\frac{SD_\alpha^2}{\alpha^2} + 5\frac{SD_{k_A}^2}{k_A^2} + \frac{SD_{k_{21}}^2}{k_{21}^2}}$

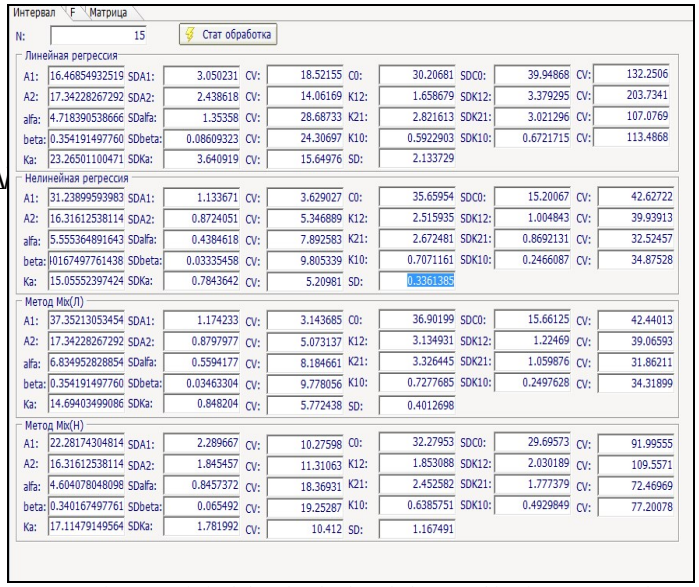


Fig. 7. Statistical data for the found pharmacokinetic parameters by several numerical methods.

An analytic proof of the existence of three solutions in the solution of the inverse problem for equation (11) and the representation of the algorithm for their finding are given in this paper. The theoretical proof of the nonuniqueness of the solution is confirmed by numerical calculations [9-16].

In the numerical solution of (51) one can find one solution for equation (11). The remaining two solutions can be determined with the help of the solution found.

V. CONCLUSION

After numerous numerical experiments in solving the inverse problem for equation (11), finding some constants through linearization is quite effective in terms of iterative

algorithms and in the accuracy of determining the parameters. Consider the case when $\lambda_2 < \lambda_1 < k_1$. Next, there given an algorithm for finding the constants of equation (11):

1. Through linearization we find the values λ_2, A_2.

2. Knowing the maximum value and using equality $C_2^{'}(t_{\max}) = 0$ consider A_1 in form $A_1 = (k_1 A_2 e_{k_1} - \lambda_2 A_2 e_{\lambda_2}) / (\lambda_1 e_{\lambda_1} - k_1 e_{k_1})$, where $e_i = e^{-it_{\max}}$.

3. After some simple transformations, we have the following equation depending on two variables k_1, λ_1:

$$C(t) = \frac{A_2 (k_1 - \lambda_2 e^{(k_1 - \lambda_2)t})}{\lambda_1 e^{(k_1 - \lambda_1)t} - k_1}$$

For the numerical implementation of the above algorithm, there is no complication. Condition $\lambda_1 < k_1$ reduces the plane of research twice. To solve the third point, we can use numerical methods for solving a system of two nonlinear equations.

When solving the inverse problem from experimental data $C_2 - t$ is complicated by the fact that the instability is added to the problem of nonuniqueness of the solution. The problem of incorrectness of the inverse problem, caused by the instability of its solution, is one of the main problems in this field of knowledge. Its severity can be reduced by the continuous improvement of the optimization procedures used and the quality of the experiment. However, completely this problem can not be solved in principle.

In Fig. 7 that the standard deviation is quite satisfactory. Also, it can be seen from Fig. 6 that the concentration curves of the preparation in the peripheral chamber are almost twice as large as the model preset (red curve) by quantitative values. This suggests that we are still far from finding the pharmacokinetic parameters correctly.

As the numerical results show, when exponential functions are used, there can be found a set of pharmacokinetic parameters that very well characterize the given experimental data. It can be seen that the concentration curves of the central chamber describe the data of exact solution taken with an error of 1%, but there is no similarity in the peripheral chamber with model pharmacokinetic parameters. They differ from each other several times. This can definitely indicate that even for simple linear models of pharmacokinetics, there is no single correct algorithm for determining or finding the pharmacokinetic parameters.

REFERENCES

[1] B.A. Urmashev, Zh.R. Ualiev, N.A. Asmanova, On some problems of solving inverse problems of the chemical kinetics of reactions with the formation of intermediate compounds. // 2) Consecutive reactions a → b → c with reversible interaction b↔d // Materials of the 4th international symposium "Combustion and Plasma Chemistry". 12-14 September 2007. P. 278-280.

[2] B.A. Urmashev, Zh.R. Ualiev, N.A. Asmanova, On some problems of solving inverse problems of the chemical kinetics of reactions with the formation of intermediate compounds. // 3) Conditions for the coincidence of the curves c = f (t) of the component in the systems a → b → c (i) and a → b → c, b↔d (ii) // Materials of the 4th international symposium «Combustion and Plasma Chemistry». 12-14 September 2007. P. 281-284.

[3] S.D. Varfolomeev, K.G. Gurevich, Biokinetics. Faire-Press, -M: 1999, -720s.

[4] M. P. Adam, Foundations in Pharmacokinetics //Copyright 2013, p.175.

[5] V.I. Yunkerov, S.G. Grigoriev, Mathematico-statistical processing of medical research data. - SPb .: VMEDA, 2002.-266 p.

[6] O.Yu. Rebrova, Statistical analysis of medical data. Application of a package of applied programs STATISTICA.-M .: MediaSfera, 2002.- 212 p.

[7] W.L. Chiou, Critical Evaluation of the Potential Error in Pharmacokinetic Studies of Using the Linear Trapezoidal Rule Method for the Calculation of the Area Under the Plasma Level-Time Curve. // J. Pharmacokin. Biopharm., 1978, 6, №. 6. -P. 539-546.

[8] I. Gaidyshev, Analysis and data processing: special reference book - St. Petersburg, Peter, 2001.-752 p.

[9] S. Leon, Yu. Andrew, Applied Biopharmaceutics and pharmacokinetics // p. 47-62, 4-th edition.

[10] L. B. Peter, R.D. Danny, Pharmacokinetics in Drug Development: Advances and Applications, volume 3. Springer, 2011, p. 78

[11] D. Z. D'Argenio, A. Schumitzky, X. Wang, Adapt 5 user's guide: Pharmacokinetic/pharmacodynamic systems analysis software. Biomedical Simulations Resource, Los Angeles, 2009.

[12] V.I. Sergienko,R. Gelliff, I.B. Bondareva, Applied pharmacokinetics: main provisions and clinical application. -M .: RAMS, 2003. -208 p.

[13] S. A. Hill, Pharmacokinetics of drug infusions. Continuing Education in Anaesthesia, Critical Care & Pain, 4(3):76–80, 2004.

[14] K.C. Yeah, K.C. Kwan, A Comparison of Numerical Integrating Algorithms by Trapezoidal, Lagrange, and Spline Approximation.// J. Pharmacokin. Biopharm., 1978, 6, №.1, -P.79-98.

[15] S.I. Kabanikhin, D.A.Voronov, O.I. Krıvorotko, A.A. Grozd, Identıfıtsıŕyemost dınamıcheskoı sıstem na prımere modeleı farmakokınetıkı ı ımmýnologıı// Sıbırskıe elektronnye matematıcheskıe ızvestııa, Tom 12, dekabr, Novosıbırsk 2015 g. – S.182-188.

[16] S.I. Kabanikhin, O.I. Krivorotko, Identification of biological models described by systems of nonlinear differential equations // Journal of Inverse and Ill-Posed Problems, Vol. 23, Iss. 5, 2015. – P. 519-527. DOI: 10.1515/jiip-2015-0072.