Optimizing Multiple Drug Administration from Depot by Applying Pharmacokinetic Concepts

Krasimira Prodanova

Department of Mathematical Analysis & Differential Equations
Faculty of Applied Mathematics and Informatics
Technical University – Sofia
8 Kl. Ohridski Blvd., 1000 Sofia, Bulgaria
E-mail: kprod@tu-sofia.bg

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Abstract: *For the multiple drug administration from therapeutic reasons it is important to maintain the concentration in the blood plasma in an appropriate range. In the present paper an optimization approach is developed to determine drug dosage regimen to achieve the desired plasma concentrations after application from depot, i.e. oral, muscular, subcutant. The developed methodology allows the optimization of both the dose and the dosage interval. Performance of the developed methodology is evaluated by computing bias and precision of the estimated trough and peak drug concentrations that are reached after dosage regimen determinations. This article focuses on an optimal impulsive control of compartment model to individualise dosage regimens of Amikacin in the context of extended dosage intervals. Amikacin is an aminoglycoside antibiotic used to treat various bacterial infections.*

Keywords: *Compartment modelling, Optimization of multiple drug administration, Individualization of drug therapy.*

Introduction

Quantitative methods for individualizing and optimizing the dosage regimen and clinically monitoring for each patient are desirable to ensure that each patient can obtain effective therapeutic benefit while minimizing undesirable side effects.

Aminoglycosides cause irreversible hearing loss and nephrotoxity. The toxic effects of aminoglycosides (Amikacin, Gentamicin, Tobramicin, Netilmicin, Kanamycin, Isepamicin, Meropenem) are dose dependent and correlate with increasing drug serum concentrations. The effectiveness and toxicity of aminoglycosides show a strong direct positive relationship with blood drug concentrations, therefore, therapy with aminoglycosides in adults is usually guided by therapeutic drug monitoring. Dosing regimens in adults have been evolved from multiple daily dosing to extended-interval dosing [15]. This evolution has also taken place in neonates [16].

For the multiple drug administration, it is important from therapeutic reasons to maintain the concentration in the blood plasma in an appropriate range. Therapeutic range is defined in terms of peak concentration (to monitor effectiveness) and trough concentration (to avoid toxicity). The common optimization methods use pharmacokinetic/pharmacodynamic concepts [18]. In [3, 7] an application of stochastic optimization and an Bayesian estimation for the appropriate dosage regimen prediction of amikacin are presented. In [10, 11, 14] are considered some problems which make possible to optimize the infusion rate input of multiple intravenous administration of drug, i.e. when the application is in the blood vessels. In the present paper an optimal impulsive control of compartment models is developed to determine dosage regimen

aiming to achieve the desired plasma concentrations after drug administration from depot, i.e. oral, muscular, subcutant, and etc.

Simple pharmacokinetic methods involve linear dosage adjustment based on peak, or on trough concentrations or on area under the concentration-time curve, or on nomograms. They are preferred methods due to their simplicity, strong pharmacodynamic rationale and prospective validation in a large population [13]. However, it does not work when the assumed fixed dose is not relevant, for example for patients with burns, cystic fibrosis, ascites, kidney or liver disease or pregnancy, because of the wide inter individual variability of aminoglycoside pharmacokinetic parameters [15].

In the present paper the measurements of Amikacin concentration in serum of the patient with kidney disease are used to individualise dosage regimens (dose per administration and/or administration interval) to achieve attaining the desired therapeutic range as quickly as possible. This article focuses on methods to individualise Amikacin dosage regimens after intramuscular application in the context of extended dosage intervals. The developed methodology allows the optimization of both the dose and the dosage interval. It uses measurements of Amikacin concentrations from two or more samples taken in the pre- and post-distributive phase during a single dosage interval. Performance of the developed methodology is evaluated by computing bias and precision of the estimated and the trough peak in Amikacin concentrations that are reached after dosage regimen determinations.

Problem statement

Let us consider two-compartment linear pharmacokinetic model with absorption, where the transfer of drug between two compartments is assumed to occur in two directions [2, 18].

Let the application of drug comes from a depot, i.e. oral, muscular, subcutant, etc. supply. The administration is regarded as an impulsive input to the gastrointestinal tract, muscle or subcutaneous tissue, etc. The compartment receiving a nonnegative input is assumed to be the first and an apparent space of drug distribution in the body containing the blood space to be the second one. The dynamics of this system is described by the following differential equations:

$$\begin{aligned} \frac{dM_1}{dt} &= -k_{12}M_1 + k_{21}M_2, \\ \frac{dM_2}{dt} &= k_{12}M_1 - (k_{20} + k_{21})M_2, \end{aligned} \tag{1}$$

where M_1 and M_2 are drug quantities correspondingly in the first and in the second compartment; k_{ij} are the parameters of the compartment model (which will be estimated using nonlinear regression).

The base compartment is the second one, M_2. Only there (in the second compartment) the drug concentration could be measured. The drug administration is applied in the first compartment and a multiple administration is assumed.

The control in the system (1) is realized as follows. In the first compartment at the moments $0 = t_1 < t_2 < ... < t_n$ the impulses ε_i are applied: $x_1(t_i^+) = x(t_i^-) + \varepsilon_i, \quad i = 0, 1, 2, ..., n$.

The sizes of the impulses ε_i correspond to the quantity of the applied drug. Since the measurement of the drug is possible only in the second compartment let us introduce also the variable

$$x_2(t) = \frac{M_2(t)}{V_2}, \tag{2}$$

where V_2 is the volume of the second compartment. Hence, $x_2(t)$ is its drug concentration. Then the system (1) can be rewritten as

$$\begin{aligned} \frac{dM_1}{dt} &= -k_{12}M_1 + k_{21}V_2x_2, \\ \frac{dx_2}{dt} &= \frac{k_{12}}{V_2}M_1 - (k_{20}+k_{21})x_2. \end{aligned} \tag{3}$$

Let us assume that the parameters $V_2, k_{20}, k_{21}, k_{12}$ are already known (this leads to parameter estimation problem and it is discussed in the next section). So one can state the following problem.

The drug administration will be multiple applied until the drug concentration reaches the value prescribed by the therapist. After this the multiple drug administration will continue, but according to the rule, that the drug concentration (again in the second compartment) will remain in the prescribed by the therapist ranges $[a, b]$ mg/ml. Obviously, there are two stages of the problem. In the first one, there exists an interval $[t_0, t_C]$, for which the drug concentration starting at zero will reach a given value *C*. In the second stage, there is an interval $[t_C, t_m]$ (actually this is the time of the active therapy) during which the concentration $x_2(t)$ has to be kept in the prescribed ranges

$$C - \delta \le x_2(t) \le C + \delta, \quad t \in [t_C, t_m], \tag{4}$$

where δ is a parameter which determines the announced prescribed ranges. In the second stage, one will divide the interval $[t_C, t_m]$, into *n* subintervals. The control is determined by ε_i – the impulses in each left end of these impulses. One will introduce the following criteria of optimality

$$F_2 = \sum_{i=N_1}^{N} \int_{t_i}^{t_{i+1}} |x_2(t) - C| dt \to \min. \tag{5}$$

The optimality criterion takes into integral account of the absolute deviation of $x_2(t)$ from the value *C*. In Eq. (5) with N_1 is denoted the index after which a stationary process state has been achieved. The additivity of the objective function F_2 allows to seek the minimum of the function (5) in each subinterval $[t_i, t_{i+1}]$ and to determine the value of ε_i – the impulse for which this minimum is achieved.

Problem solution

The characteristic equation of the system (1) is

$$r^2 + (k_{20} + k_{12} + k_{21})r + k_{12}k_{20} = 0$$

with roots

$$\alpha = r_1 = \frac{1}{2}\left[-(k_{20} + k_{12} + k_{21}) + \sqrt{(k_{20} + k_{12} + k_{21})^2 - 4k_{20}k_{21}}\right],$$
$$\beta = r_2 = \frac{1}{2}\left[-(k_{20} + k_{12} + k_{21}) - \sqrt{(k_{20} + k_{12} + k_{21})^2 - 4k_{20}k_{21}}\right].$$

For the *i*-th interval $t \in [t_i, t_{i+1}]$, $i = 1, 2, \ldots$, the solution of the system (4) has the form

$$\begin{aligned} M_1^{(i)}(t) &= e^{\alpha(t-t_i)}C_{1i} + e^{\beta(t-t_i)}C_{2i}, \\ x_2^{(i)}(t) &= \frac{(\alpha + k_{12})e^{\alpha(t-t_i)}}{V_2 k_{21}}C_{1i} + \frac{(\beta + k_{12})e^{\beta(t-t_i)}}{V_2 k_{21}}C_{2i}, \end{aligned} \tag{6}$$

where the constants of integration C_{1i}, C_{2i} are determined by

$$C_{1i} = \left(\left(x_1^{(i-1)}(t_i) + \varepsilon_i\right)(\beta + k_{12}) - x_2^{(i-1)}(t_i)k_{21}\right)\frac{1}{\beta - \alpha},$$
$$C_{2i} = \left(x_2^{(i-1)}(t_i)k_{21} - \left(x_1^{(i-1)}(t_i) + \varepsilon_i\right)(\alpha + k_{12})\right)\frac{1}{\beta - \alpha}.$$

For the first subinterval one has

$$x_2^{(1)}(t) = \frac{\varepsilon_i(\beta + k_{12})(\alpha + k_{12})}{(\beta - \alpha)V_2 k_{21}}\left(e^{\alpha t} - e^{\beta t}\right). \tag{7}$$

An application to a real data

The solution of the considered problem essentially depends on the parameters of the system the volume V_2 and the rates k_{20}, k_{21}, k_{12}. For a specific clinical case (patient with a serious tissue infection and renal failure), after single intramuscular administration of antibiotic Amikacin, in our disposition were six experimental data points $\left(t_j, x_2(t_j)\right)$, $j = 1, 2, \ldots, 6$ of plasma concentration $x_2(t)$. Three samples are taken in the pre-distributive and three – in the post-distributive phase during a single dosage interval. By using the method of nonlinear regression to the data, we estimate the individual pharmacokinetics parameters for the patient $k_{20} = 0.1\ \text{h}^{-1}, k_{12} = 6.5\ \text{h}^{-1}, k_{21} = 1.5\ \text{h}^{-1}$. The maximal feasible impulse (dose) for drug administration is $\varepsilon_0 = 80$ mg.

The parameter V_2 appears like a scale factor and has a subsidiary role. Its value is estimated to be $V_2 = 10$ l. For the first stage of the stated problem (for the particular assumed data) one finds the solution, $x_2 = x_2(t)$, shown at the Fig. 1.

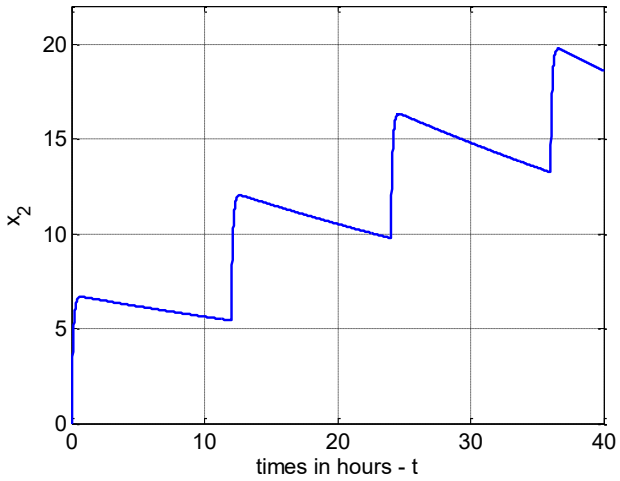

Fig. 1 The concentration $x_2 = x_2(t)$ for the first stage of the problem

This solution is obtained also when taking into account the following details. It is assumed multiple drug administration in impulses with maximal feasible impulse ε_0 and with the conventional acquired application every 12 hours. As it can be seen from Fig. 1, where the concentration in the second compartment enters into the prescribed by the therapist zone about the value of C = 15 mg/ml. Therefore, one will assume t_C = 24 hours and will pass over the second stage of the problem.

In the second stage of the problem one will seek such control which will maintain the concentration $x_2 = x_2(t)$, $t \in [t_C, t_m]$ (for the time t_m the value $t_m = 120$ hours is assumed) in the ranges $15 - \delta \le x_2(t) \le 15 + \delta$, $t \in [24, 120]$. One will divide the interval $[24, 120]$ into 8 subintervals – this means that again the conventional application of every 12 hours is assumed. The control is determined by ε_i $(i = 1, 2, ..., 8)$ – the impulses in each left end of these impulses.

The optimality criterion (5) takes into integral account of the absolute deviation of $x_2(t)$ from the value 15 mg/ml. In Fig. 2 the graphic of such optimally determined concentration $x_2 = x_2(t)$, $t \in [0, 120]$ is shown. The values of the corresponding impulses ε_i (in mg) for the successive subintervals are:

80; 80; 80; 41.0256; 39.5897; 39.5897; 38.1538; 39.5897; 39.5897; 39.5897.

The maximal deviation of $x_2 = x_2(t)$ is $X_{i\max} = \max\left|x_2(t) - C\right|$, $t \in [t_i, t_{i+1}]$.

In the almost stationary process after t_4, $X_{i\max}$ is 1.6825 mg/ml, or in percentages with respect to C = 15 mg/ml is $\delta = 11.22\,\%$. The region, where the concentration $x_2(t)$ is placed, is bounded by the upper bound $C_{\max} = 16.69$ mg/ml and by the lower bound $C_{\min} = 13.31$ mg/ml.

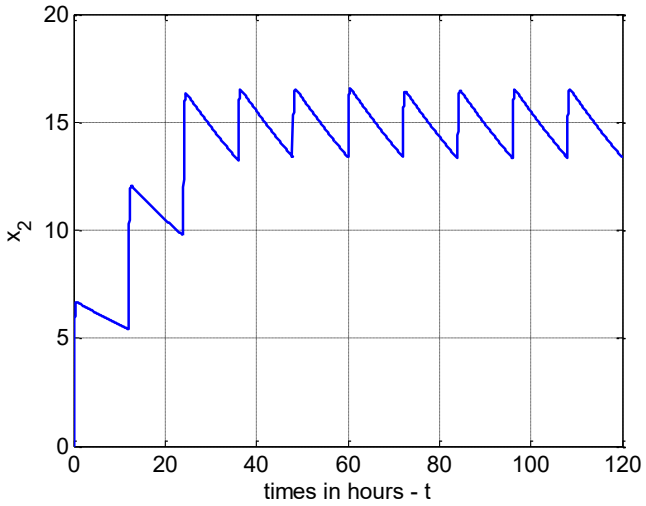

Fig. 2 The concentration $x_2 = x_2(t)$, $t \in [0, 120]$

Fig. 2 demonstrates convincingly how after the first stage, following an appropriate control policy, the concentration $x_2 = x_2(t)$ is kept in the fixed bounds (4). On Fig. 3 the detailed behavior of the graph of the criterion F_2 in time before and after a dose ε is shown. One can see very clearly how the considered function reaches its minimum in an inner point. At the minimum of the drop down function it is applied a new dose (impulse ε) which causes respective growth of the criterion. As sooner this impuls is applied, as higher the growth in F_2 will start upward.

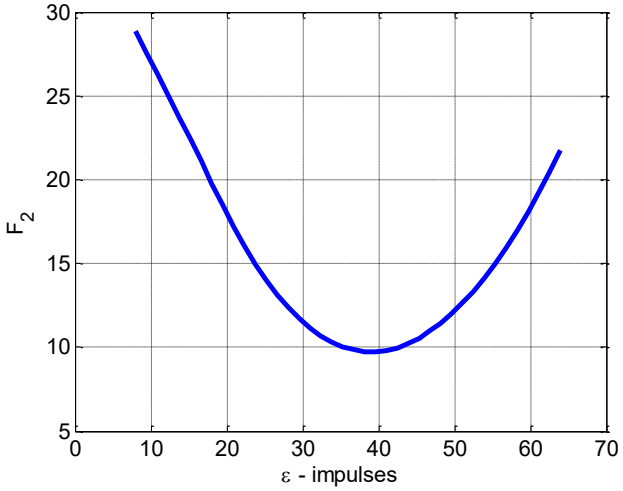

Fig. 3 Graph of the criterion F_2 in time befor and after a dose

We obtained a solution under the assumption that the drug is applied every 12 hours. Let us change this assumption and look for a solution of the stated problem under the assumption of drug application every 24 hours. Now we shall increase the time t_m in order to

reach clearly determined stationary process. One will choose $t_m = 168$ hours and then instead of 8 (like in the previous case) there will be 6 subintervals $[t_i, t_{i+1}]$ (after t_C = 24). There is actually the same optimization problem where only one of the parameters has been changed.

On Fig. 5 the graph of the concentration $x_2 = x_2(t), \ t \in [0, 168]$ is presented for the changed conditions. The values of the impulses ε_i (in mg) for the corresponding successive subintervals are as follows:

80; 80; 80; 80; 80; 80; 78.1538; 78.1538.

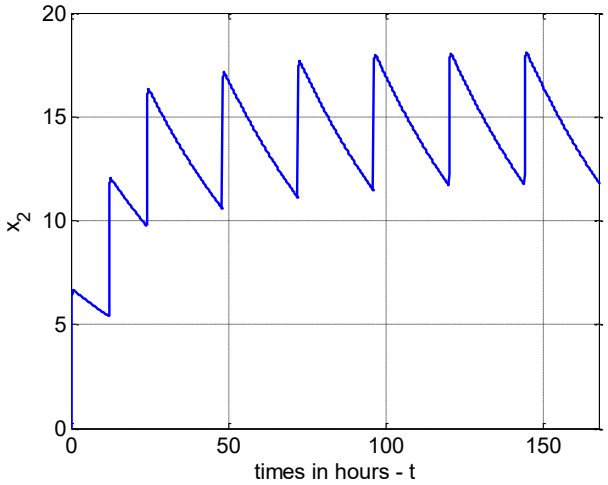

Fig. 4 The concentration $x_2 = x_2(t)$ for drug application once in every 24 hours

It can be seen that in four of the six subintervals the applied impulses achieve their maximal feasible values. This means that for these subintervals the minimum of the objective function F_2 is reached at the end of the subinterval. On Fig. 5 it is shown the graph of the criterion F_2 for subinterval $t \in [t_5, t_6]$. For the cases when the minimum of the objective function F_2 is reached for an inner point, the corresponding picture is analogous to Fig. 4 and then the optimal impulse ε occurs to be less as the maximal feasible value of 80.

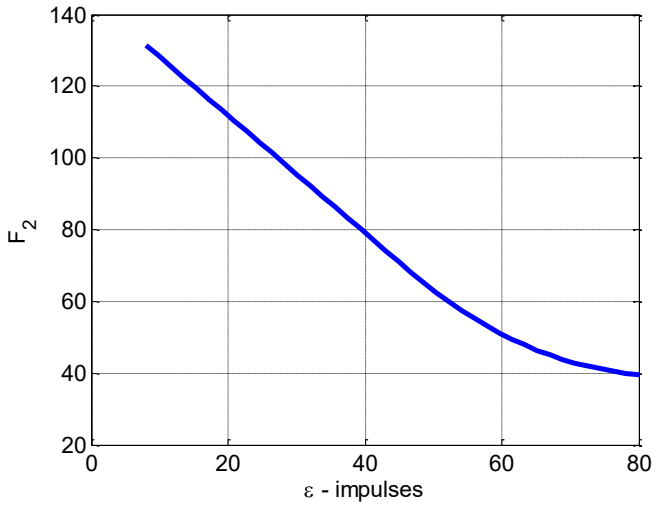

Fig. 5 Graph of the criterion F_2 for subinterval $t \in [t_5, t_6]$

For the stationary process after t_4, the maximal deviation of $x_2 = x_2(t)$ is $X_{i\max} = 3.8675$ mg/ml, or in percentages with respect to C it is $\delta = 25.78\,\%$. The region where the concentration $x_2(t)$ is supposed to stay for the drug to do the job is bounded between the upper value $C_{\max} = 18.9$ mg/ml and the lower value $C_{\min} = 11.1$ mg/ml.

It is naturally to understand that the violations of the drug limitations leads to enlarged variation of the concentration $x_2 = x_2(t)$ in the second compartment. The therapist is who should decide whether the ranges of this variation are admissible or not.

In order to clarify these questions an intermediate case is also considered. It assumes more frequent drug dose application every 18 hours. For more convenient displacement of the subintervals we assume $t_m = 150$ hours. Then the subintervals $[t_i, t_{i+1}]$ are 7 (after t_C = 24). On Fig. 6 it is shown the graph of the concentration $x_2 = x_2(t)$, $t \in [0, 150]$ determined for this new frequency conditions. Now the corresponding optimal values of the impulses (dose applications) ε_i (in mg) for the successive subintervals are as follows:

80; 80; 80; 67.0769; 57.8462; 59.6923; 57.8462; 59.6923; 57.8462.

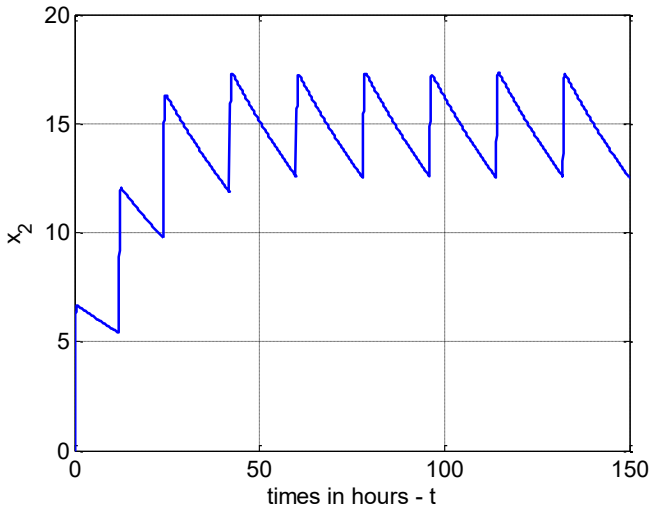

Fig. 6 The concentration $x_2 = x_2(t)$ for drug application every 18 hours

Based on the above explanations, now it is clear that in all subintervals (after t_C = 24), the minimum of the objective function F_2 is reached for an inner point of the subinterval.

The maximal deviation $x_2 = x_2(t)$ for the stationary process after t_4 is 2.50 mg/ml. In percentages with respect to the value C of the targeted concentration it is $\delta = 16.68\,\%$. The region where the concentration $x_2(t)$ is located is bounded by the upper limit $C_{\max} = 17.5$ mg/ml and by the lower limit $C_{\min} = 12.5$ mg/ml.

At the end, for more completeness of the investigation, let us consider also the case of drug application in frequency every 8 hours. Here, we shall diminish the horizon of considerations because the stationary process is reached considerably earlier rather than in the cases considered

with larger interval of dosage application. Therefore, we assume that $t_m = 96$ hours. The first stage will be not changed, i.e. this more frequently drug application occurs after t_C = 24. The number of subintervals in this case is 9.

On Fig. 7 it is shown the graph of the optimal concentration $x_2 = x_2(t)$, $t \in [0, 96]$ for drug application every 8 hours.

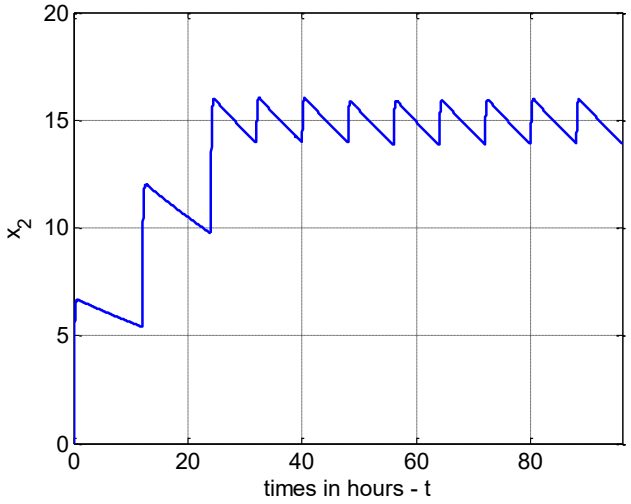

Fig. 7 The concentration $x_2 = x_2(t)$ for drug application every 8 hours

The corresponding values of the impulses ε_i (in mg) for the successive subintervals are:

80; 80; 75.9; 26.46; 26.46; 24.62; 26.46; 26.46; 26.46; 26.46; 26.46.

As it can be expected, now the variation of the concentration $x_2(t)$, for the stationary process after t_C = 24, (which it is very clearly demonstrated in Fig. 7) is the smallest one. The maximal deviation of $x_2 = x_2(t)$ for the stationary process after t_3 is 1.15 mg/ml. In percentages with respect to the value C this deviation is $\delta = 7.69\,\%$. The region, where the concentration $x_2(t)$ is located, is bounded by the upper bound $C_{\max} = 16.15$ mg/ml and by the lower bound $C_{\min} = 13.85$ mg/ml.

Discussion

In this paper the mathematical-based design for optimization and individualization of the therapy is presented. We use mechanism-based pharmacokinetic-pharmacodynamic (PK/PD) modelling, which is the standard computational technique for simulating drug treatment of infectious diseases with the potential to enhance our understanding of drug treatment outcomes, drug deployment strategies, and dosing regimens. In essence [1, 6, 19], this approach incorporates existing PK/PD parameters estimates into differential equations to calculate the decline in drug concentration after treatment.

In [3, 4, 8, 9, 14, 16, 17] and many others research papers the application of Aminoglycosides is considered to be intravenous (IV) bolus (i.e. without resorption phase) or Intravenous

infusion (IV inf.). IV infusion is characterized with complete (100%) systemic drug resorption and rate of drug absorption is controlled by infusion rate.

In contrast to these studies, in our work the application of Amikacin is Intramuscular (IM), i.e. the drug is injected into skeletal muscle. IM absorption is rapid from aqueous solution, is slow from oil solutions and different rates of absorption are depending on muscle group and blood flow. Because of this the differential equations describing PK models after IV infusions and after IM administration are different. For IV infusion administration, rate constant of absorption is known while rate constant of absorption for IM or oral application is estimated using measurements of plasma samples in the pre-distributive phase [1, 2, 18].

One may see the differences in the differential equations for the two-compartment pharmacokinetic model with resorption and thus of the two-compartment pharmacokinetic model for IV infusion in [15] or in Table 4 of [3].

For estimation of PK parameters we use 3 individual plasma samples in the pre-distributive phase, which give us possibility to estimate the absorption rate constant and three – after, for estimation of the rate constants of distribution and elimination.

In the most of the research papers dealing with IV bolus and IV infusion regimen optimization problem, the estimation of the rate constants of distribution and elimination is based on one individual measurement – a through concentration or on two – peak and through concentrations [8]. After that some researchers used this data as initial for program procedure [4] or for dosing guideline [5, 12], or for Bayesian PK estimation software [3, 7], where Bayesian prior probability is based on the population pharmacokinetics of the given drug. The program in [4] calculates an ideal maintenance dose, dosing interval and estimated steady-state peak, based on one-compartment model without absorption.

So, the majority of the studies have focused on the optimization of therapy with aminoglycosides using PK models for IV bolus and IV infusion administration.

To the best of our knowledge, the dosage regimen optimization problem defined in terms of general two-compartment pharmacokinetic model with absorption and a solution approach which uses a scenario-based optimization formulation that minimizes a risk metric has not been reported in literature till now.

Conclusion

This study presents a very good opportunities for illustration of an optimization approach in solving pharmacokinetic problems, related to the support of drug concentration in desirable limits (after administration from depot), where the drugs are most effective. The found quantitative results allow to find exact optimal dosage solutions for any preliminary determined intervals of drug application.

For the considered particular case (how to individualise Amikacin dosage regimens in the context of determination of doses and dosage intervals) the main results are: for drug application every 12 hours the optimal deviation of the supported concentration from the prescribed one is $\delta^{(12)} = 11.2\,\%$. For drug application every 24 hours, this percentage is $\delta^{(24)} = 25.8\,\%$. Further, for 18 and 8 hours the corresponding numbers are $\delta^{(18)} = 16.7\,\%$ and $\delta^{(8)} = 7.7\,\%$. The result

that variability decreases with the shortening the intervals of dose application are similar to the other authors [1, 6, 8, 9, 17].

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Prof. Krasimira Prodanova, Ph.D.
E-mail: kprod@tu-sofia.bg

Krasimira Prodanova graduated in Mathematics at Sofia University "St. Kliment Ohridski", Bulgaria, received Ph.D. degree (1995) from the Technical University – Sofia with thesis about statistical models in pharmacokinetics. At present, she is a Professor at the Technical University – Sofia. She has more than 100 publications in reviewed and indexed journals and proceedings of international conferences, 9 books and 2 book chapters. Her scientific interests are in the fields of mathematical modeling in pharmacokinetics and medicine, estimation of the parameters of stochastic models, drug response models, survival analysis and optimization problems.