Optimizing Multiple Drug Administration from Depot by Applying Pharmacokinetic Concepts

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Abstract: For the multiple drug administration it is important from therapeutic reasons to maintain the concentration in the blood plasma in an appropriate range. The effectiveness and toxicity of antibiotics and especially 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. In the present paper an optimization approach was developed to determine Amikacin dosage regimen to achieve the desired plasma concentrations after application from depot. The developed methodology allows the optimization of both the dose and the dosage interval. Performance of the developed methodology was evaluated by computing bias and precision of the estimated trough and peak Amikacin concentrations that were reached after dosage regimen determinations.

Key-Words: optimization of multiple drug administration, individualization of drug therapy

1 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. The toxic effects of aminoglycosides 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 [1]. Dosing regimens in adults have been evolved from multiple daily dosing to extended-interval dosing. This evolution has also taken place in neonates [2].

For the multiple drug administration, it is important from therapeutic reasons to maintain the concentration in the blood plasma in an appropriate range. The common optimization methods use pharmacokinetic/pharmacodynamic concepts [3]. In [4,5] an application of Bayesian estimation for the appropriate dosage regimen prediction of Amikacin is presented. In [6,7,8] are considered some problems which make possible to optimize the infusion rate input or of multiple intravenous administration of drug.

In the present paper an optimal impulsive control of compartment models was developed to determine Amikacin dosage regimen to achieve the desired plasma concentrations after drug administration from depot. Measurements of Amikacin concentration in serum are used to individualise dosage regimens (dose per administration and/or administration interval) to achieve attaining the desired therapeutic range as quickly as possible. Therapeutic range is defined in terms of peak concentration (to monitor effectiveness) and trough concentration (to avoid toxicity). This article focuses on methods to individualise Amikacin dosage regimens in the context of extended dosage intervals. Simple pharmacokinetic methods involve linear dosage adjustment based on peak or trough concentrations or area under the concentration-time curve, or nomograms. They are preferred methods due to their simplicity, strong pharmacodynamic rationale and prospective validation in a large population. However, it does not work when the fixed dose assumed is not relevant, for example for patients with burns, cystic fibrosis, ascites or pregnancy, because of the wide interindividual variability of aminoglycoside pharmacokinetic parameters [1]. The developed methodology allows the optimization of both the dose and the dosage interval, but

requires 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 was evaluated by computing bias and precision of the estimated of the trough and peak Amikacin concentrations that were reached after dosage regimen determinations.

2 Problem Formulation

Let us consider two- compartment linear pharmacokinetic model, where the transfer of drug between two compartments is assumed to be occur in two directions [3].

Let the application of drug is from depot i.e. oral, muscular, subcutant and etc. The administration is regarded as an impulsive input to the gastrointestinal tract or muscle tissue or 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 (Fig.1). Then the dynamics of this system is described by the following differential equations:

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

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

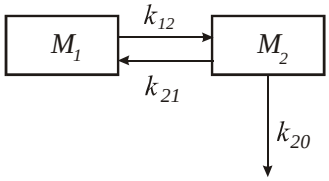

Fig.1 Two compartment model

The base compartment is the second one. 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:

$$(2)\quad x_1(t_i^+) = x(t_i^-) + \varepsilon_i, \quad i = 0,1,2,...,n\,.$$

The size of these impulses - ε_i corresponds to the quantity of the applied drug. Since the measurement of the drug is possible only in the second compartment let us denote also

$$(3)\quad x_2(t) = \frac{M_2(t)}{V_2}$$

where V_2 is the volume of the second compartment and $x_2(t)$ - its drug concentration. Then the system (1) will be rewritten as

$$(4)\quad \begin{aligned} \frac{dM_1}{dt} &= -k_{12}M_1 + k_{21}V_2x_2 \\ \frac{dx_2}{dt} &= \frac{k_{12}}{V_2}M_1 - (k_{20}+k_{21})x_2 \end{aligned}$$

Let us assume that the parameters $V_2, k_{20}, k_{21}, k_{12}$ are already known (this lead 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 till the drug concentration reaches the value prescribed by the therapist. After this the multiple drug administration will continue but with rule that the drug concentration (again in the second compartment) will remain in the prescribed by the therapist ranges. Obviously, there are two stages of the problem. In the first one – there exists an interval $[t_1, t_0]$ for which the drug concentration starting at zero will reach a given value - C_0; and in the second stage - there is an interval $[t_1, t_0]$ (actually this is the time of the active therapy) – the concentration $x_2(t)$ has to be kept in the ranges – $C_0 - \delta \le x_2(t) \le C_0 + \delta, \quad t \in [t_0, \quad t_m]$, where δ is a parameter which determines the announced prescribed ranges.

3 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

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

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

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

$$M_1^{(i)}(t) = \quad e^{\alpha(t-t_i)}C_{1i}+e^{\beta(t-t_i)}C_{2i},$$

$$x_2^{(i)}(t) = \frac{(\alpha+k_{12})e^{\alpha(t-t_i)}}{V_2k_{21}}C_{1i} \quad + \quad \frac{(\beta+k_{12})e^{\beta(t-t_i)}}{V_2k_{21}}C_{2i},$$

where the constants of integration C_{1i}, C_{2_i} 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

$$(6)\qquad x_2^{(1)}(t) = \frac{\varepsilon_i(\beta+k_{12})(\alpha+k_{12})}{(\beta-\alpha)V_2k_{21}}\left(e^{\alpha t}-e^{\beta t}\right).$$

The solution of the considered problem essentially depends on the parameters of the system - $V_2, k_{20}, k_{21}, k_{12}$. 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 $(t_j, x_2(t_j)),\ j=1,2,...,6$ of plasma concentration $x_2(t)$. Smaples are taken in the pre- and post-distributive phase during a single dosage interval. By using the method of nonlinear regression to the data, we estimate the individual pharmacokinetics parameters of the patient $k_{20}=0.1[\mathrm{h}^{-1}];\ \mathrm{k}_{12}=6.5[\mathrm{h}^{-1}];\ \mathrm{k}_{21}=1.5[\mathrm{h}^{-1}]$. The maximal feasible impulse (dose) for drug administration is $\varepsilon_0 = 80\,\mu g$.

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. 2.

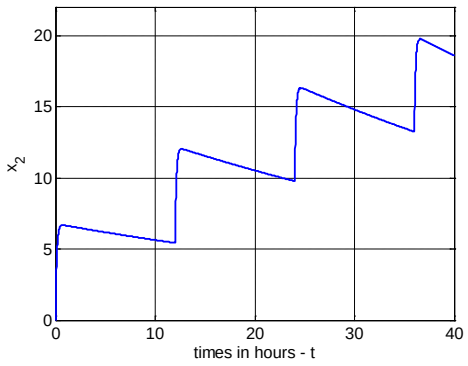

Fig.2 The concentration $x_2 = x_2(t)$ for the first stage of the problem

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 $C_0 = 15\mu g/ml$. Therefore, one will assume $t_0 = 24$ 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 $x_2 = x_2(t),\quad t\in[t_0,t_m]$ (for the time t_m the value t_m =120 is assumed) in the ranges

$$(7)\qquad C_0-\delta \le x_2(t) \le C_0+\delta,\quad t\in[t_0,\quad t_m].$$

One will divide the interval $[t_0,t_m]$ into 8 subintervals – this means that again the conventional application of every 12 hours is assumed. The control is determined by ε_i - the impulses in each left end of these impulses. One will introduce the following criteria of optimality –

$$(8)\qquad F_2 = \sum_{i=N_1}^{N}\int_{t_i}^{t_{i+1}}\left|x_2(t)-C_0\right|dt \to \min.$$

The same optimality criteria was introduced in [10,11] and it takes into integral account of the deviation of $x_2(t)$ about the value C_0. In (8) with N_1 is denoted the index after which a stationary process has been achieved.

The additivity of the objective function F_2 allows to seek the minimum of the function (8) in each subinterval $[t_i,t_{i+1}]$ and to determine the value of ε_i - the impulse for which this minimum is achieved. In Fig.2 the graphic of the such

determined concentration $x_2 = x_2(t), \quad t \in [0, t_m]$ is shown. The values of the corresponding impulses ε_i (in μg) 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 $X_{i\max} = \max\left|x_2(t) - C_0\right|, \quad t \in [t_i, t_{i+1}]$.

In the almost stationary process after t_4 is 1.6825 $\mu g / ml$, or in percentages with respect to C_0 is $\delta = 11.22\,\%$. The region where the concentration $x_2(t)$ is placed is bounded by the upper bound $C_{max} = 16.69$ $\mu g / ml$ and by the lower bound $C_{min} = 13.31$ $\mu g / ml$.

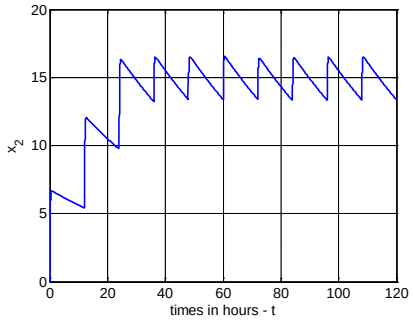

Fig.3 The concentration $x_2 = x_2(t)$, $t \in [0, t_m]$

Fig.3 demonstrates convincingly how after the first stage following an appropriate control law, the concentration $x_2 = x_2(t)$ is kept in the fixed bounds (7). In Fig.4 is shown the graph of the criterion F_2 as a function of varying impulses ε in some chosen subinterval. One can see very clearly how the considered function reaches its minimum in an inner point.

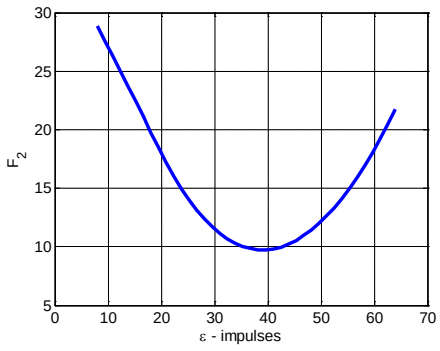

Fig.4 Graph of the criterion F_2 as a function of varying impulses ε

One has 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 $t_0 = 24$). There is actually the same optimization problem where only one of the parameters has been changed.

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

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

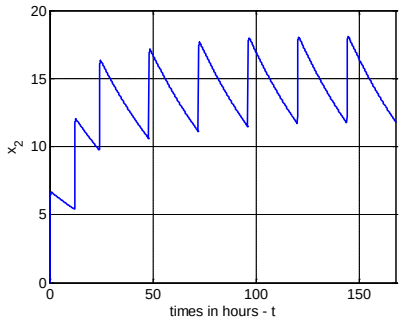

Fig.5 The concentration $x_2 = x_2(t)$ for drug application every 24 hours

It can be seen that in four of the six subintervals the applied impulses with their maximal feasible values. This means that for these subintervals the minimum of the objective function F_2 is reached at the border of the subinterval.

In Fig.6 the graph of the of the criterion F_2 as a function of the varying impulses ε for such subinterval is shown. 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.

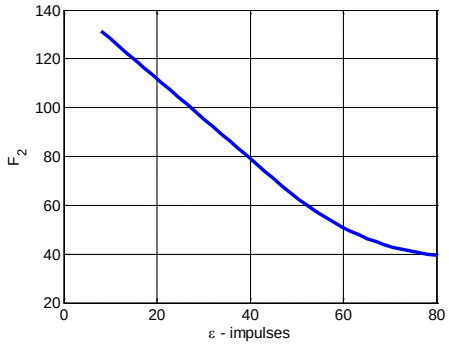

Fig 6 Graph of the criterion F_2 for subinterval $t \in [t_5, t_6]$

The maximal deviation of $x_2 = x_2(t)$ is $X_{i\max} = \max\left|x_2(t) - C_0\right|$, $t \in [t_i, t_{i+1}]$, for the stationary process after t_4 is 3.8675 $\mu g / ml$, or in percentages with respect to C_0 - $\delta = 25.78\,\%$. The region where the concentration $x_2(t)$ is placed is bounded by the upper bound $C_{\max} = 18.9$ $\mu g / ml$ and by the lower bound $C_{\min} = 11.1$ $\mu g / ml$.

As it was naturally to be expected the thin out of the drug application leads to an enlarged variation of the concentration $x_2 = x_2(t)$ in the second compartment. The therapist is one to decide whether the ranges of this variation are admissible or not.

In order to clarify these questions an intermediate case will also be considered when the drug is applied every 18 hours. For more convenient replacement of the subintervals will be assumed that $t_m = 150$ hours. Then the subintervals $[t_i, t_{i+1}]$ are 7 (after $t_0 = 24$). In Fig.7 is shown the graph of the concentration $x_2 = x_2(t)$, $t \in [0, t_m]$ determined for this new conditions. Now the corresponding values of the impulses ε_i (in μg) for the successive subintervals are as follows:

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

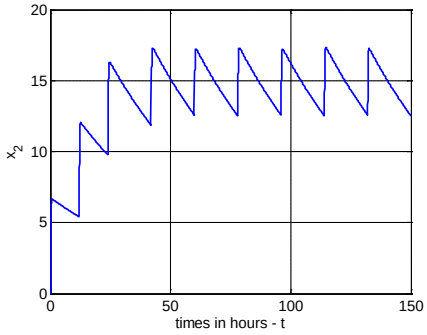

Fig. 7 The concentration $x_2 = x_2(t)$ for drug application every 18 hours

Based on the above explanations, now it is clear that in all subintervals (after $t_0 = 24$), the minimum of the objective function F_2 is reached for an inner point of the subinterval.

The maximal deviation of $x_2 = x_2(t)$ - $X_{i\max} = \max\left|x_2(t) - C_0\right|$, $t \in [t_i, t_{i+1}]$ for the stationary process after t_4 is 2.50 $\mu g / ml$, or in percentages with respect to the value C_0 is $\delta = 16.68\,\%$. The region where the concentration $x_2(t)$ is placed is bounded by the upper bound $C_{\max} = 17.5\,\mu g / ml$ and by the lower bound $C_{\min} = 12.5\,\mu g / ml$.

At the end, for more completeness of the investigation, let us consider also the case of drug application 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 so far. Therefore, will be assumed that $t_m = 96$ hours. The first stage will be not changed, i.e. this more frequently drug application occurs after $t_0 = 24$. The number of subintervals in this case (after $t_0 = 24$) is 9.

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

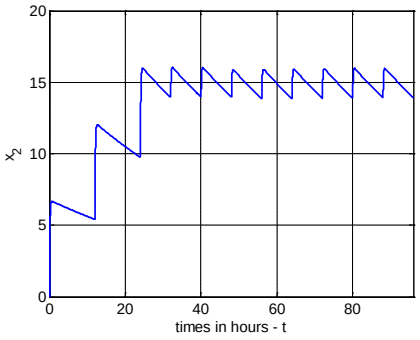

Fig.8 The concentration $x_2 = x_2(t)$ for drug application every 8 hours

Now the corresponding values of the impulses ε_i (in μg) for the successive subintervals are as follows:

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 $t_0 = 24$, (which it is very clearly demonstrated

in Fig.8) is the smallest one. The maximal deviation of $x_2 = x_2(t) : X_{i\max} = \max\left|x_2(t) - C_0\right|, t \in [t_i, t_{i+1}]$ for the stationary process after t_3 is 1.15 $\mu g / ml$, or in percentages with respect to the value C_0 is $\delta = 7.69\,\%$. The region where the concentration $x_2(t)$ is placed is bounded by the upper bound $C_{\max} = 16.15\,\mu g / ml$ and by the lower bound $C_{\min} = 13.85\,\mu g / ml$.

4 Conclusion

The investigations described above give a very good opportunities illustration optimization approach for solving the stated pharmacokinetic problems related with the individualization of the therapy is applied. The quantitative results found allow to evaluate the demonstrated solutions. Let us repeat the main results: for drug application every 12 hours the parameter δ which determines the deviation of the obtained concentration with respect to the prescribed ones is $\delta^{(12)} = 11.22\,\%$. For drug application every 24 hours, this percentage is $\delta^{(24)} = 25.78\,\%$. Further, for 18 and 8 hours the corresponding numbers are $\delta^{(18)} = 16.68\,\%$ and $\delta^{(8)} = 7.69\,\%$.

Acknowledgements

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