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RESEARCH ARTICLE

Computational Analysis of Pharmacokinetic Behavior of Ampicillin

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The objective of this study was to perform a computational analysis of the pharmacokinetic behavior of ampicillin, using data from the literature. A method based on the theory of dynamic systems was used for modeling purposes. The method used has been introduced to pharmacokinetics with the aim to contribute to the knowledge base in pharmacokinetics by including the modeling method which enables researchers to develop mathematical models of various pharmacokinetic processes in an identical way, using identical model structures. A few examples of a successful use of the modeling method considered here in pharmacokinetics can be found in full texts articles available free of charge at the website of the author, and in the example given in the this study. The modeling method employed in this study can be used to develop a mathematical model of the pharmacokinetic behavior of any drug, under the condition that the pharmacokinetic behavior of the drug under study can be at least partially approximated using linear models.

Keywords: pharmacokinetics, oral administration, dynamic system, mathematical model.

Introduction

The antibiotic drug ampicillin was developed in 1961 [1,2]. It is commonly used to treat respiratory tract infections, urinary tract infections, meningitis, salmonella infections, and endocarditis. Besides that, ampicillin has been used also to prevent group B streptococcal infection in newborns, and also as an anticancer drug [1-3]. During the last decades, the research domain of systems engineering emerged as a domain of fundamental importance with a great impact on several fields of sciences, including the field of pharmacokinetics, see for example the following studies [4-21] and references therein. Previous examples showing an advantageous use of the modeling method used in this study can be found in the full text articles available online, which can be downloaded, free of charge from the following web page of the author: http://www.uef.sav.sk/advanced.htm

Ampicillin is administered mostly by mouth. Besides that, ampicillin is also administered by injection into a muscle, and/or intravenously. Common side effects of ampicillin include rash, nausea, and diarrhea. The objective of this study was to perform a computational analysis of the pharmacokinetic behavior of ampicillin in patient no.1, using the data from the study published previously [2].

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Materials and Methods

For modeling purposes, a mathematical modeling method based on the theory of dynamic systems was employed [4-21]. The development of a mathematical model for computational analysis of the pharmacokinetic behavior of ampicillin in patient no. 1 [2] was performed in the following successive steps:

- In the first step, the pharmacokinetic dynamic system, denoted by *H*, was defined for patient no. 1, using:

1) the Laplace transform of the mathematical function

describing the ampicillin administration to patient no. 1, denoted by *I(s)*, and considered the mathematically relevant ampicillin input to the body of patient no. 1, and/or to the pharmacokinetic dynamic system defined [22]
2) the Laplace transform of the mathematical function describing the plasma concentration-time profile of ampicillin of patient no. 1, denoted by *C(s)* , and considered as the mathematically relevant output of the dynamic system defined. In the whole text of this study, the lower case letter "*s*" denotes the complex Laplace variable.
- In the second step, the following simplifying assumptions were made:
a) initial conditions of the pharmacokinetic dynamic system defined were zero;
b) pharmacokinetic processes occurring in the body after the ampicillin administration were linear and time invariant;
c) ampicillin concentrations were the same throughout all subsystems of the pharmacokinetic dynamic system defined (where subsystems were integral parts of the pharmacokinetic dynamic system defined);
d) no barriers to the distribution and/or elimination of ampicillin existed.
- In the third step, pharmacokinetic dynamic system defined was used to mathematically describe static and dynamic properties of the pharmacokinetic behavior of ampicillin in the patient no. 1 [23-25].
- In the fourth step, the transfer function, denoted by of the pharmacokinetic dynamic system defined was derived using:
1) the Laplace transform of the mathematical function describing the ampicilin administration to patient no.1, denoted by, and considered the mathematically relevant ampicillin input to the patient's body and/or to the dynamic system defined [22] and
2) the Laplace transform of the mathematical function describing the plasma concentration-time profile of ampicillin, denoted by, and considered the mathematically relevant output of the dynamic system defined:

$$H(s) = \frac{C(s)}{I(s)}. \qquad (1)$$

- In the fifth step, the pharmacokinetic dynamic system defined was described with the transfer function, denoted by H(s).
For modeling purposes, the computer program CTDB [4] and the transfer function model, denoted by described by **Eq. (2)** were used:

$$H_M(s) = G\frac{a_0 + a_1 s + \ldots + a_n s^n}{1 + b_1 s + \ldots + b_m s^m}. \qquad (2)$$

On the right-hand-side of **Eq. (2)** is the Padé approximant [26,27] of the transfer function model $H_M(s)$ is the model parameter called a gain of a dynamic system $a_1 \ldots a_n$, $b_1 \ldots b_n$, are additional model parameters, and n is the highest degree of the nominator polynomial, and m is the highest degree of the denominator polynomial, where $n < m$ [4-21].
- In the sixth step, the transfer function *H(s)* was converted into equivalent frequency response function, denoted by $F(i\omega_j)$[26].
- In the seventh step, the non-iterative method published previously [26] was used to develop a mathematical model of the frequency response function $F_M(i\omega_j)$ of Patient no.1and to obtain point estimates of parameters of the frequency response function model $F_M(i\omega_j)$ in the complex domain. The frequency response function model $F_M(i\omega_j)$ used in this study is described by the following equation:

$$F_M(i\omega_j) = G\frac{a_0 + a_1 i\omega_j + \ldots + a_n (i\omega)^n}{1 + b_1 i\omega_j + \ldots + b_m (i\omega_j)^m}. \qquad (3)$$

Analogously as in **Eq. (2)**, is the highest degree of the numerator polynomial of the frequency response function model $F_M(i\omega_j)$, m is the highest degree of the denominator polynomial of the frequency response function model $F_M(i\omega_j)$, $n < m$ is the imaginary unit, and ω is the angular frequency in **Eq. (3)** [26].
- In the eighth step, the frequency response function model $F_M(i\omega_j)$ was refined using the Monte-Carlo and the Gauss-Newton method in the time domain.
- In the ninth step, the Akaike information criterion [28] was used to select the best the model of the frequency response function $F_M(i\omega_j)$ among all frequency response function modes developed [6-20].
- In the final step, 95 % confidence intervals were calculated for all parameters of the best frequency response function model $F_M(i\omega_j)$ developed. In the following text, the pharmacokinetic dynamic system was simply called the dynamic system.
After the development of a mathematical model of the dynamic system, the following potentially important pharmacokinetic variables of ampicillin were determined: the elimination half-time of ampicilin, denoted by $t_{½}$ the area under the plasma concentration-time profile of ampicillin from time zero to infinity, denoted by $AUC_{0\to\infty}$

and total body clearance of ampicillin, denoted by *Cl*.

Results and discussion

The data of patient no.1 from the study by Colburn [2] were arbitrarily chosen for this study. The best-fit third-order model $F_M(i\omega_j)$ selected using the Akaike's information criterion [28] is described by the following equation:

$$F_M(i\omega_j) = G\frac{a_0 + a_1 i\omega_j}{1 + b_1 i\omega_j + b_2 i\omega_2 + b_3 i\omega_3}. \quad (4)$$

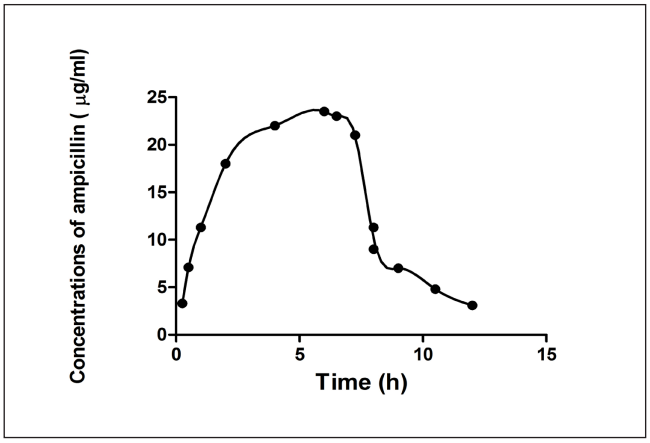

Figure 1. Plasma concentration-time profile of ampicillin of Patient no.1 (points) [2] and the developed model for patient no.1 (line).

Table 1. Point estimates of parameters of the model developed for patient no.1 [2]

Model parameters	Point estimates of model parameters ± standard deviation
a_0	1.00 ± 0.11
a_1	1.52 x 10^3 ± 0.12
b_1	2.03 x 10^2 ± 70.1
b_2	1.01 x 10^4 ± 0.09
b_3	2.22 x 10^5 ± 0.01

As shown in **Figure 1**, the model developed provided an adequate fit to the observed serum concentration-time profile of ampicillin of patient no.1 [2]. Point estimates of the parameters a_0, a_1, b_1, b_2, b_3 of the best model $F_M(i\omega_j)$ are listed in **Table 1**. Model-based estimates of potentially important pharmacokinetic variables of ampicillin are listed in **Table 2**.

The dynamic system used in this study was a mathematical object, without any physiological significance. It was used to mathematically approximate static and dynamic properties of the pharmacokinetic behavior of ampicillin [23-25] in patient no.1 [2]. The modeling method used in this study was described in detailed in the studies published previously, authored and/or co authored by the author of this study [4,6-20]. As in previous studies, the development of a mathematical model of the pharmacokinetic dynamic system defined was based on the known input and output of the dynamic system defined was used in this study. In general, if a dynamic system is modeled using a transfer function model, as it was the case in the this study (see **Eq. (2)**), then the accuracy of the model depends on the degrees of the polynomials of the transfer function model used to fit the data [4,6-20]. The model parameter called the gain is also called gain coefficient, or gain factor. A parameter gain is defined as a relationship between a magnitude of an output of a dynamic system to a magnitude of an input to a dynamic system in steady state [6-20]. Or in other words, a model parameter gain of a dynamic system is a proportional value that shows a relationship between a magnitude of an output to a magnitude of an input of a dynamic system in the steady state. The pharmacokinetic meaning of a parameter gain depends on the nature of a dynamic system under study.

Table 2. Potentially important pharmacokinetic variables of ampicillin of patient no.1 [2]

Potentially important pharmacokinetic variables of ampicillin	Estimates of potentially important pharmacokinetic variables of ampicillin ± standard deviation
C_{max} (μg/mL)	23.5 ± 1.55
$t_{½}$ (h)	0.74 ± 0.11
Cl (mL/min)	61.1 ± 2.38
V_{ss} (L)	13.1 ± 1.04

C_{max}– maximum ampicillin concentration in plasma; $t_{1/2}$ – elimination half life of ampicillin; Cl – clearance of ampicillin; V_{ss} – apparent volume of distribution of ampicillin

The non-iterative method published in the study [26] and used in this study allows one to identify an optimal structure of frequency response models very quickly. It is a great advantage of the non-iterative method [26], because this significantly speeds up the development of frequency response models. The reason for conversion of $H_M(s)$ to $F_M(i\omega_j)$ can be explained as follows: the variable: "s" in the transfer function model $H_M(s)$ in **Eq. (1)** and **Eq. (2)** is a complex Laplace variable, while the angular frequency "ω" in **Eq. (3)** and **Eq. (4)** is a real variable,

what is suitable for modeling purposes.

The mathematical model developed in this study sufficiently approximated static and dynamic properties [23-25] of the pharmacokinetic behavior of ampicillin in patient no.1 [2]. Therefore, the mathematical model developed, successfully described the serum concentration-time profile of ampicilin of patient no.1 [2]. Modeling pharmacokinetic behavior of ampicilin was performed in this study only with the aim to present the further example of the successful use of the modeling method [4] in pharmacokinetics, without any relation to the therapeutic use of ampicillin. Frequency response functions are complex functions, therefore modeling must be performed in the complex domain. Moreover, modeling methods used to develop model frequency response functions are computationally intensive, and for accurate modeling they require at least a partial knowledge of the theory of dynamic system, and an abstract way of thinking about dynamic systems under study.

The principal difference between traditional pharmacokinetic modeling methods and modeling methods that are based on the theory of dynamic systems can be explained as follows: the former methods are based on mathematical modeling plasma (or blood) concentration-time profiles of drugs administered, however the latter methods are based on mathematical modeling dynamic relationships between a mathematically described drug administration and a mathematically described resulting plasma (or blood) concentration-time profile of a drug administered.

Modeling methods based on the theory of dynamic system exhibit the following advantages when compared with compartment modeling method [29-39];

1) key requirements of compartment modeling methods are not necessary;

2) specific model structures (in general unknown) are not necessary;

3) abstract assumptions of homogenous instantaneously well mixed compartments are also not necessary. On the other hand, modeling methods based on the theory of dynamic system exhibit few apparent disadvantages: the development of mathematical models is not a simple task; the use of the modelling methods considered here requires at least partial knowledge of the theory of dynamic systems and mathematics.

The transfer function model $H_M(s)$ and the model of the frequency response function $F_M(i\omega_j)$ have been implemented in the computer program CTDB [4]. A demo version of the computer program CTDB is available at: http://www.uef.sav.sk/advanced.htm.

Conclusion

The modelling method used in this study is universal; therefore it can be used to model any linear dynamic system, not only in the field of pharmacokinetics but also in many other scientific or practical fields. This study repeatedly showed that a modelling method based on the theory of dynamic systems can be advantageously used in pharmacokinetics. As it follows from this study, the integration of key pharmacokinetic concepts and bioengineering concepts bioengineering is a good and efficient way to study dynamic processes in pharmacokinetics, because such integration combines mathematical rigor with biological insight.

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