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Research Article

Mathematical Model of the Pharmacokinetic Behavior of Theophylline

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Abstract

Objective: To provide a further example which showed that a non-traditional mathematical modeling method based on the theory of dynamic systems can be successfully used for mathematical modeling pharmacokinetics.

Method: The current study is a companion piece of the study by Kasuya., *et al*. [1]; published in December 1985 issue of the Journal of Pharmacokinetics and Biopharmaceutics, therefore the data published in the study cited here was used. An advanced mathematical modeling method based on the theory of dynamic systems was employed for modeling purposes. The program named CTDB described in the study by Dedík., *et al*. published in September 2007 issue of the Journal Diabetes Research and Clinical Practice was employed for modeling purposes.

Conclusion: The mathematical model developed, using the data available in the study by Kasuya., *et al*. [1], successfully described the pharmacokinetic behavior of theophylline. The modeling method used in this study is universal, comprehensive, and flexible. Therefore, it can be used in the development of mathematical models not only in the field of pharmacokinetics but also in several other scientific and practical fields.

Keywords: *Pharmacokinetics; Mathematical model; Dynamic system*

Abbreviations

ADME: Absorption/Distribution/Metabolism/Excretion; CTDB: Clinical Trials Data Base

Introduction

It is well known that a compartment modeling method (i.e. one of the most frequently used modeling methods in pharmacokinetics) is based on mathematical modeling plasma and/or blood concentration-time profiles of administered drugs. In contrast, modeling methods that use computational tools from the theory of dynamic systems are based on mathematical modeling dynamic relationships between mathematically described drug administrations and mathematically described body responses to administered drugs (e.g. blood and/or plasma concentration time profiles of administered drugs), see an explanatory picture and full text journal articles, available completely free of charge at the following web sites of the author: http://www.uef.sav.sk/durisova.htm and http://www.uef.sav.sk/advanced.htm.

Theophylline, also known as 1,3-dimethylxanthine, is a methylxanthine drug. It is frequently used for therapy of patients with respiratory diseases such as chronic obstructive pulmonary disease and asthma under a variety of brand names. Theophylline as a member of the xanthine family, it bears structural and pharmacological similarity to theobromine and caffeine. A small amount of theophylline is one of the products of caffeine metabolic processing in the liver [1-7].

The current study is a companion piece of the study by Kasuya., *et al*. published in December 1985 issue of the Journal of Pharmacokinetics and Biopharmaceutics [1]. Therefore, the data available in the study cited here was used.

The main objective of the current study was to provide a further example showing a successful use of an advanced mathematical modeling method based on the theory of dynamic systems in mathematical modeling in a pharmacokinetic study [8-22]. Previous examples showing an advantageous use of the modeling method used in the current study can be found in the full text journal articles available online, which can be downloaded, completely free of charge from the web sites mentioned previous paragraph.

An additional objective of the current study was to motivate researchers in pharmacokinetics to use an alternative modeling method to those modeling methods which are traditionally used in pharmacokinetics.

Methods

An advanced mathematical modeling method based on the theory of dynamic systems was employed to develop a mathematical model of the pharmacokinetic behavior of an orally administered theophylline, using the raw data available in the study published by Kasuya., *et al* [1].

The development of a mathematical model of the pharmacokinetic behavior of theophylline [1-7] was conducted in the following successive steps:

(1) The definition of an ADME-related dynamic pharmacokinetic system [8-22], denoted by H, using: the Laplace transform of the mathematically described serum concentration-time profile of theophylline, denoted by $C(s)$, and the Laplace transform of the mathematically described oral administration of theophylline [1], denoted by $I(s)$. In the definition of the ADME-related dynamic pharmacokinetic system, the profile $C(s)$ and profile $I(s)$ was used as the output and input, respectively, of the ADME-related dynamic pharmacokinetic system H [8-23].

(2) An introduction of the following simplifying assumptions: a) initial conditions of the ADME-related dynamic pharmacokinetic system were zero; b) all processes mathematically described by the ADME-related dynamic pharmacokinetic system were linear and time invariant [9-22]; c) concentrations of theophylline were the same throughout all subsystems of the ADME-related dynamic pharmacokinetic system, (where each subsystem was an integral part of the ADME-related dynamic pharmacokinetic system); d) all processes in the body after the theophylline oral administration were linear and time invariant, e) no barriers to the distribution and/or elimination of theophylline existed;

(3) The static and dynamic properties of the dynamic pharmacokinetic behavior of orally administered theophylline [1, 24-26] were described with the ADME-related dynamic pharmacokinetic system;

(4) The transfer function, denoted by $H(s)$, of the ADME-related dynamic pharmacokinetic system was derived, using the profiles C(s) and I(s), see Equation (1).

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

(5) The ADME-related dynamic pharmacokinetic system was described with the transfer function H(s) in the complex domain.

Throughout the current study the lower-case letter "s" denotes the complex Laplace variable [9-22]. In the following text, the ADME-related dynamic pharmacokinetic system was simply called the dynamic system defined.

(6) A mathematical model of the dynamic system was developed using the computer program named CTDB [15] and the transfer function

model $H_M(s)$ described by the following equation:

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

On the right-hand-side of Equation (2) is the Padé approximant [27,28] of the mathematical model of the transfer function $H_M(s)$, G is an estimator of the model parameter called the gain of the dynamic system, $a_1, \cdots a_n, b_1, \cdots b_m$ are additional model parameters, and n is the highest degree of the nominator polynomial, and m is the highest degree of the denominator polynomial, n is the highest degree of the nominator polynomial, and $n < m$ (see Equation 2) [9-22].

(7) The transfer function $H(s)$ was converted into equivalent frequency response function, denoted by $F(i\omega_j)$ [28].

(8) The non-iterative method described in the study published previously [28] was used to develop a mathematical model of the frequency response function $F_M(i\omega_j)$ and to determine point estimates of parameters of the model of the frequency response function $F_M(i\omega_j)$ in the complex domain. The model of the frequency response function $F_M(i\omega_j)$ used in the current study is described by the following equation:

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

Analogously as in Equation (2), n is the highest degree of the numerator polynomial of the model of the frequency response function $F_M(i\omega_j)$, m is the highest degree of the denominator polynomial of the mathematical model of the frequency response function $F_M(i\omega_j)$, $n \leq m$, i is the imaginary unit, and $\grave{u}$ is the angular frequency in Equation (3).

The Akaike information criterion, modified for the use in the complex domain [9,29] was employed to select the best mathematical model of the frequency response function $F_M(i\omega_j)$ and to determine point estimates of the parameters of the best mathematical model of the frequency response function $F_M(i\omega_j)$.

Finally, the Monte-Carlo and the Gauss-Newton method [30,31] were used to refine the mathematical model of the frequency response function $F_M(i\omega_j)$ and to determine 95 % confidence intervals of the parameters of the best mathematical model of the frequency response function $F_M(i\omega_j)$ in the time domain.

After the development of the best mathematical model $F_M(i\omega_j)$ of the dynamic system, the following primary pharmacokinetic variables of theophylline were determined: the elimination half-time of theophylline, denoted by $t_{1/2}$, the area under the serum concentration-time profile of theophylline from time zero to infinity, denoted by, $AUC_{0-\infty}$, and total body clearance of theophylline, denoted by ***Cl.*** The mathematical model of the transfer function $H_M(s)$ and the mathematical model of the frequency response function $F_M(i\omega_j)$ are implemented in the computer program CTDB [15]. A demo version of the computer program CTDB is available at the following web site: http://www.uef.sav.sk/advanced.htm.

Results and Discussion

The best-fit third-order mathematical model $F_M(i\omega_j)$ selected with the Akaike information criterion, modified for the use in the complex domain [9,29], is described by the following equation:

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

As seen in Figure 1, the mathematical model developed provided an adequate fit to the concentration data of theophylline available in the study [1]. Estimates of the model parameters a_0, a_1, b_1, b_2, b_3 are in Table 1. Model-based estimates of primary pharmacokinetic variables of theophylline are in Table 2.

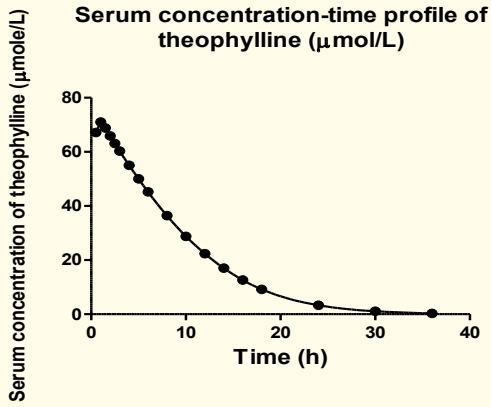

Figure 1: *Observed arterial serum concentration time profile of theophylline and the description of the observed profile with the developed model of the dynamic system describing the pharmacokinetic behavior of theophylline [1].*

Model parameters	Estimates of model parameters	(95% CI)
G (h.l^{-1})	0.0046	0.006 to 0.012
a_0 (-)	0.923	0.825 to 1.024
a_1 (min)	69.15	45.12 to 72.38
b_1 (min)	421.88	391.73 to 462.02
b_2 (min^2)	6043.61	7028.59 to 6059.33
b_3 (min^3)	3478275.74	3478271.05 to 3678280.33

Table 1: *Parameters of the third-order model of the dynamic system describing the pharmacokinetic behavior of orally administered theophylline [1].*

Pharmacokinetic variables	Estimates of pharmacokinetic variables
The half-time of theophylline $t_{1/2}$ (hod)	1.5 ± 0.4*
Clearance of theophylline (ml/min)	103.1 ± 15.3
Renal clearance of theophylline (ml/min)	74.1 ± 5.1
Body clearance of theophylline (ml/min)	218 ± 8.1
Elimination half-life of theophylline (hr)	51.6 ± 5.4
Distribution volume of theophylline (l)	681 ± 9.5
$AUC_{0\to\infty}$ (ng.h/ml)	26.95

Table 2: *Model-based estimates of pharmacokinetic variables of orally administered theophylline [1].*

**standard deviation*

The dynamic system used in this study was a mathematical object, without any physiological significance. It was used to mathematically describe static and dynamic properties of the dynamic pharmacokinetic behavior of the orally administered theophylline [1,24-26]. The method used in the current study was described in detail in the studies published previously [9-22], authored and/or co-authored by the author of this study, therefore a description of the modeling method used was not given here. The mathematical model developed was validated utilizing the theophylline data from the study by Kasuya., *et al* [1].

Analogously as in the studies published previously [9-22], the development of a mathematical model of the dynamic system was based on the known input and output of the dynamic system in the current study. In general, if a dynamic system is investigated using a transfer function model, as it was the case in this study (see Eq. (2)), then the accuracy of the model depends on degrees nominator and denominator polynomial of the mathematical model of the frequency response function $F_M(i\omega_j)$, see for example the following studies [9-22], and references therein.

The parameter gain is called also gain coefficient, or gain factor. In general, 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. Or in other words, a 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 an investigated dynamic system in the steady state.
http://www.uef.sav.sk/advanced.htm.

The non-iterative method described in the study published previously [28] and used in this study method allows rapid identification of an optimal structure of a mathematical model of a frequency response function. This is a great advantage of the method used, because it significantly speeds up the process of developing a mathematical model $F_M(i\omega_j)$ of a frequency response function $F(i\omega_j)$.

The reason for conversion of $H_M(s)$ to $F_M(i\omega_j)$ has been explained in studies published previously [9-22], therefore such an explanation was not given here.

This study again showed that mathematical and computational tools from the theory of dynamic systems can be successfully used in mathematical modeling in pharmacokinetics. Frequency response functions are complex functions; therefore, their modeling must be performed in the complex domain. The 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 investigated dynamic systems.

The principal difference between traditional pharmacokinetic modeling methods and modeling methods that use of mathematical and computational tools from the theory of dynamic systems has been explained in the studies published previously [9-22]. See the full text articles and an explanatory example available free of charge at: http://www.uef.sav.sk/advanced.htm.

The computational and modeling methods that use computational and modeling tools from the theory of dynamic systems can be used for example for adjustment of a drug (or a substance) dosing aimed at achieving and then maintaining required drug (or a substance) concentration–time profile in patients see, for example, the following study [12]. Moreover, the methods used in the current study can be used for safe and cost-effective individualization of dosing of a drug or a substance, for example using computer-controlled infusion pumps [32]. This is very important for an administration of a clotting factor to a hemophilia patient, as exemplified in the simulation study [12].

The advantages of the modeling method used in this study are evident here: The models developed overcome well known limitations of compartmental models: For the development and use of the models considered in this study, an assumption of well-mixed spaces in the body (in principle unrealistic) is not necessary. The basic structure of the models developed using computational and modeling tools from the theory of dynamic systems, is universal, therefore it is broadly applicable to develop mathematical models not only in the field of pharmacokinetics but also in several other scientific and practical fields. From a point of view of pharmacokinetic community, an advantage of the models developed using computational tools from the theory of dynamic systems is that the models considered here emphasize dynamical aspects [19] of the pharmacokinetic behavior of a drug in a human or an animal body. Transfer functions of dynamic systems are not unknown in pharmacokinetics; see for example the following studies [33-34]. In pharmacokinetics, transfer functions are usually called disposition functions [35,36].

This study again tried to motivate researchers working in the field of pharmacokinetics to use of an alternative modeling method, namely a modeling method based on the theory of dynamic systems in the development of pharmacokinetic (mathematical) models instead of traditional pharmacokinetic method.

The mathematical models developed and used in this study successfully described the pharmacokinetic behavior of theophylline [1]. The modeling method used in this study is universal, comprehensive and flexible and thus it can be applied to a broad range of dynamic systems in the field of pharmacokinetics and in many other scientific or practical fields. To see the previous examples illustrating the successful use of the modeling method employed in the current study please visit the author's web site (an English version): http://www.uef.sav.sk/advanced.htm. This study showed again that an integration of key concepts from pharmacokinetic and bioengineering is a good and efficient way to study dynamic processes in pharmacokinetics, because such integration combines mathematical rigor with biological insight.

The principal difference between traditional pharmacokinetic modeling methods and modeling methods that use of mathematical and computational tools from the theory of dynamic systems can be explained as follows: the former methods are based on mathematical modeling of plasma (or blood) concentration-time profiles of administered drugs, however the latter methods are based on mathematical modeling of a dynamic relationships between a mathematically described drug administration and a mathematically described resulting plasma (or blood) concentration-time profile of a drug administered. Pharmacokinetics of theophylline has been described in several studies previously, therefore theophylline was used only as an example in the current study.

Conflict of Interest

There is no conflict of interest.

About the author

The author is a researcher affiliated with the Institute of Experimental Pharmacology and Toxicology, the Department of Pharmacology of Inflammation Slovak, Academy of Sciences Bratislava, 84104 Slovak Republic. Her main research interest is to some extant outside

her education, because it involves investigations of various dynamic systems in pharmacokinetics, using mathematical models. However, during her work in pharmacokinetics for several years, she successfully utilized her knowledge of mathematics, based on her engineering education, what is necessary for the development of accurate mathematical models in pharmacokinetics. For more information about the modeling methods used by the author and their use in pharmacokinetic studies, please visit the author's web page at: www.uef.sav.sk/durisova.htm.

Note

The author worked as a researcher and contractor in the 6FP-Project "Network of Excellence: Biosimulation - A New Tool in Drug Development, contract No. LSHB CT-2004-005137"and in the 7FP-Project "Network of Excellence: Virtual Physiological Human". Both projects were established by the European Commission. Author worked also in several previous COST program actions. This work of the author in several international projects led to the preparation of this study.

At present, the author precipitates in the Action BM1204 of the COST program entitled: An integrated European platform for pancreas cancer research: from basic science to clinical and public health interventions for a rare disease.

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