Mathematical Model Of The Pharmacokinetic Behavior Of Phenytoin

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The current study is dedicated to Diploma engineer Juraj Kajan. To generations of students in Bratislava, Diploma engineer Juraj Kajan was an excellent teacher of mathematics, to generations of students in Bratislava. Students in Bratislava could derive knowledge from his lectures and through his personal advice and vivid discussions.

***Abstract*—The objective of the current study was to provide a further example which shows that a non-traditional mathematical modeling method based on the theory of dynamic systems can be successfully used for mathematical modeling pharmacokinetics. The current study is a companion piece of the study by Melikian et al.; published in April 1977 Issue of the Journal Pharmacokinetics and Biopharmaceutics. Therefore, the data published in the study cited here were 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. The mathematical models developed, successfully described plasma concentration-time profiles of phenytoin available in the study by Mlikian et al. The current study contains a brief description of the modeling method used along with the results obtained that clearly showed the usefulness of the modeling method employed. Taken together, the current study revealed again that modeling and computational tools from the theory of dynamic systems can be successfully used in a pharmacokinetic study.**

Keywords— Pharmacokinetics; Mathematical model; Dynamic system

Abbreviations used: ADME: absorption/ distribution/ metabolism/excretion; CTDB: Clinical Trials Data Base

Introduction

In 1938, phenytoin was introduced an anticonvulsant. Intravenous phenytoin becomes available in 1958 for the treatment status epilepticus. Since phenytoin introduction for therapeutic use, pharmacological properties of phenytoin (including phenytoin pharmacokinetics) have been extensively investigated. Therefore, an investigation of pharmacokinetic behavior of phenytoin in normal human volunteers was not the main objective of the current study.

On the contrary, the main objective of the current study was to give a further example, which shows a successful use of an advanced mathematical modeling method based on the theory of dynamic systems in mathematical modeling in a pharmacokinetic study [2-16]. The phenytoin data [1] were used with the goal to create an example. Previous examples showing an advantageous use of the modeling method used in the current study can be found in the several full text journal articles that are available online, and are downloadable completely free of charge from the web sites mentioned in the previous paragraph.

The 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 for mathematical modeling in pharmacokinetics.

Methods

An advanced mathematical modeling method based on the theory of dynamic systems was employed to develop mathematical models of the pharmacokinetic behavior of an orally administered phenytoin to human subjects, using the data available in the study published by Melikian *et al.* [1].

The development of mathematical models of the pharmacokinetic behavior of phenytoin [1] in human subjects was performed in the following successive steps [3-16]:

In the first step of the model development process, ADME-related dynamic pharmacokinetic systems [17-19], were defined using: the Laplace transforms of the mathematically described plasma concentration-time

profiles of phenytoin of human subjects, and the Laplace transforms of the mathematically described oral administration of phenytoin [1, 3-16],

In the second step of the model development process, the following simplifying assumptions were made: a) initial conditions of the ADME-related dynamic pharmacokinetic systems were zero [1,3-16]; b) all processes mathematically described by the ADME-related dynamic pharmacokinetic systems were linear and time invariant [3-16]; c) concentrations of phenytoin were the same throughout all subsystems of an ADME-related dynamic pharmacokinetic systems, where each subsystem was an integral part of an ADME-related dynamic pharmacokinetic system.

In the third step of the model development process, the static and dynamic properties of the dynamic pharmacokinetic behavior of orally administered phenytoin [1, 20-22] were described with the ADME-related dynamic pharmacokinetic systems;

In the fourth step of the model development process, the transfer functions, of the ADME-related dynamic pharmacokinetic systems were derived in the complex domain.

In the fifth step of the model development process, the ADME-related dynamic pharmacokinetic systems were described with the transfer functions in the complex domain.

In the following text, the ADME-related dynamic pharmacokinetic systems were simply called the dynamic systems.

In the sixth step, of the model development process, mathematical models of the dynamic systems were developed using the computer program named CTDB [3-16].

In the sixth step of the model development process, the transfer functions were converted into equivalent frequency response functions [24]. The non-iterative method described in the study published previously [24] was used to develop mathematical models of the frequency response functions and to determine point estimates of parameters of the models of frequency response functions in the complex domain.

The Akaike information criterion, modified for the use in the complex domain [4,25] was employed to select the best mathematical models of the frequency response functions After that, point estimates of the parameters of the best mathematical models were determined. Finally, the Gauss-Newton and the Monte-Carlo method [26,27] were used to refine the best models of the frequency response functions and to determine 95 % confidence intervals of the parameters of the best models of the frequency response functions in the time domain.

After the development of the best mathematical models of the dynamic systems investigated, the following potentially important variables for the phenytoin pharmacokinetics were determined: the elimination half-time of phenytoin, denoted by $t_{1/2}$, the area under the serum concentration-time profile of phenytoin from time zero to infinity, denoted by, $AUC_{0\text{-}\infty}$, and total body clearance of phenytoin, denoted by Cl.

The mathematical model of the transfer function and the mathematical model of the frequency response function are implemented in the computer program CTDB [9]. A demo version of the computer program CTDB is available at the following web site of the author: http://www.uef.sav.sk/advanced.htm.

Results

Figures 1-6 show observed plasma concentration time profiles of phenytoin and the descriptions of the observed profiles with the developed models of the dynamic systems describing the dynamic pharmacokinetic behavior of orally administered phenytoin [1]. As seen in Figures 1-6, the mathematical models developed provided adequate fits for all concentration data of phenytoin available in the study [1]. The mathematical models developed were validated against the phenytoin data available the study by Milikian *et al.* [1].

In the end, model-based estimates of potentially important variables for phenytoin pharmacokinetics were determined. The resulting potentially important pharmacokinetic variables are in Table 1.

Discussion

The dynamic systems used in this study were mathematical objects, without any physiological significance. They were used to mathematically describe static and dynamic properties of the dynamic pharmacokinetic behavior of the orally administered phenytoin [1, 20-22]. The method used in the current study was described in detail in the studies published previously [3-16], authored and/or co authored by the author of this study, therefore a description of the modeling method used was not given in the current study. The mathematical models developed were validated against the phenytoin data available the study by Milikian *et al.* [1].

Analogously as in the studies published previously [9-22], the development of mathematical models of the dynamic system investigated was based known inputs and outputs of the dynamic system investigated in the current study

The non-iterative method described in the study published previously [24] and used in the current study 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 of frequency response functions.

The reason for conversion of the transfer function models to frequency function models has been explained in studies published previously [4-16], therefore, such an explanation was not given in the current study.

The current 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 mathematical models of 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 [3-16]. The full text articles published previously 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 simulation study [6]. 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 [6, 27]. This is very important for an administration of a clotting factor to a hemophilia patient, as exemplified in the simulation study [6].

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 the current 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 dynamic aspects [**Error! Reference source not found.**-**Error! Reference source not found.**] 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 [**Error! Reference source not found.**-30]. In pharmacokinetics, transfer functions are usually called disposition functions [31,32].

The current 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 model developed and used in this study successfully described the pharmacokinetic behavior of phenytoin [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.

It is well known that compartment modeling methods (*i.e*. the most frequently used modeling methods in pharmacokinetics) are based on mathematical modeling plasma and/or blood concentration-time profiles of drugs administered to human subjects and/or to animals [1]. In contrast, modeling methods that use modeling and computational tools from the theory of dynamic systems are based on mathematical modeling dynamic relationships between mathematically described drug inputs into bodies of human subjects and/or animals and mathematically described responses of bodies of human subjects and/or animals to administered drugs (*e.g.* blood or plasma concentration time profiles of administered drugs), see an explanatory picture and several full text journal articles, which are 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.

Conclusions

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. Analogously as the previous studies authored and/or coauthored by the author of the current study, the current study showed usefulness of modeling and computational tools from the theory of dynamic systems in pharmacokinetics.

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, 841 04 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, potential readers of the current study are invited to visit the author's web page at: http://www.uef.sav.sk/durisova.htm and http://www.uef.sav.sk/advanced.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 seven previous COST program actions. This work of the author in several international projects led to the preparation of this study.

At present, the author participates 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, and starts her work in the Action CA15222 of the COST program entitled: European Network for cost containment and improved quality of health care.

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Potentially important pharmacokinetic variables of phenytoin	Estimates of potentially important pharmacokinetic variables of phenytoin
The half-time ($t_{1/2}$) (hod)	5.1 ± 0.4*
Clearance (Cl) (L/h/kg)	1.50
Elimination half-life (hr)	51.6±5.4
Distribution volume (l)	681±9.5
$AUC_{0\to\infty}$ (μg.hr/ml)	26.95

*standard deviation

Table 1: Model-based estimates of pharmacokinetic variables of orally administered phenytoin [1].

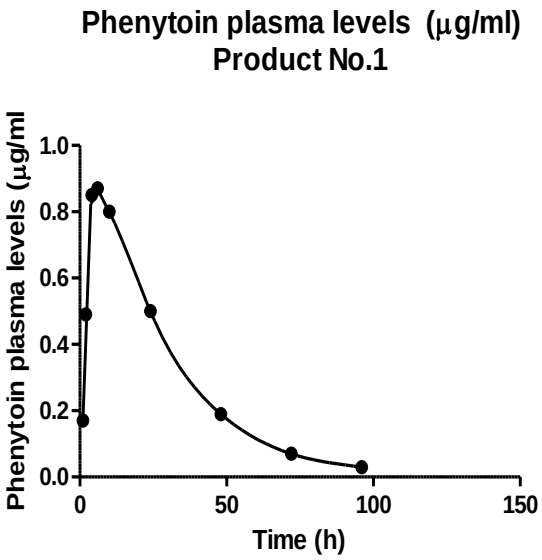

Figure 1: Observed plasma concentration time profile of phenytoin and the description of the observed profile with the developed model of the dynamic system describing the dynamic pharmacokinetic behavior of orally administered phenytoin [1].

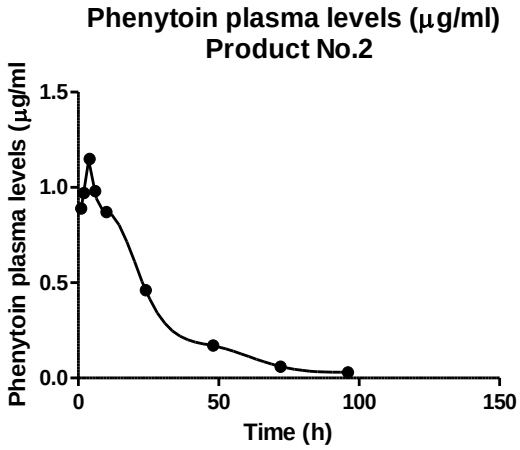

Figure 2: Observed plasma concentration time profile of phenytoin and the description of the observed profile with the developed model of the dynamic system describing the dynamic pharmacokinetic behavior of orally administered phenytoin [1].

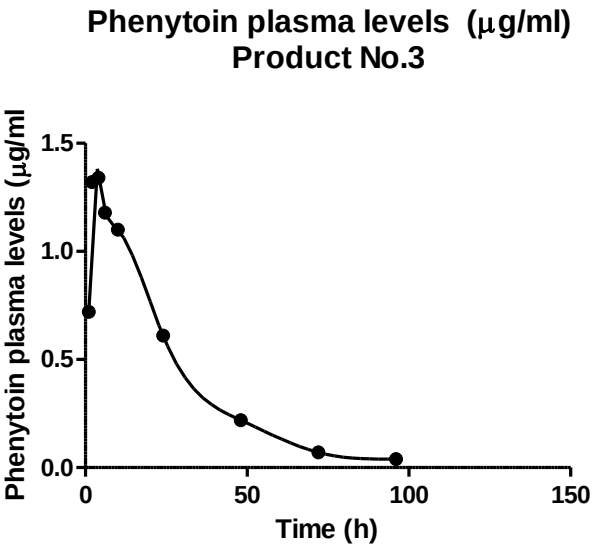

Figure 3: Observed plasma concentration time profile of phenytoin and the description of the observed profile with the developed model of the dynamic system describing the dynamic pharmacokinetic behavior of orally administered phenytoin [1].

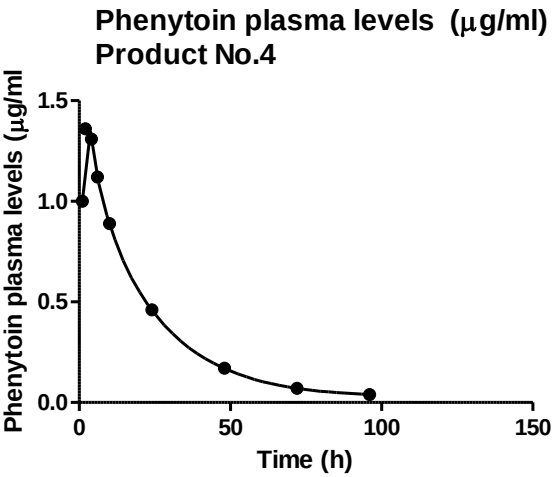

Figure 4: Observed plasma concentration time profile of phenytoin and the description of the observed profile with the developed model of the dynamic system describing the dynamic pharmacokinetic behavior of orally administered phenytoin [1].

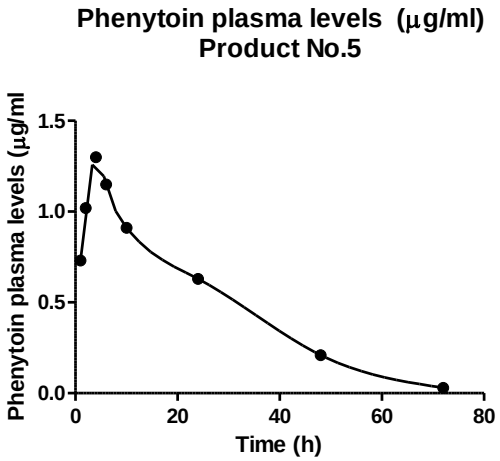

Figure 5: Observed plasma concentration time profile of phenytoin and the description of the observed profile with the developed model of the dynamic system describing the dynamic pharmacokinetic behavior of orally administered phenytoin [1].

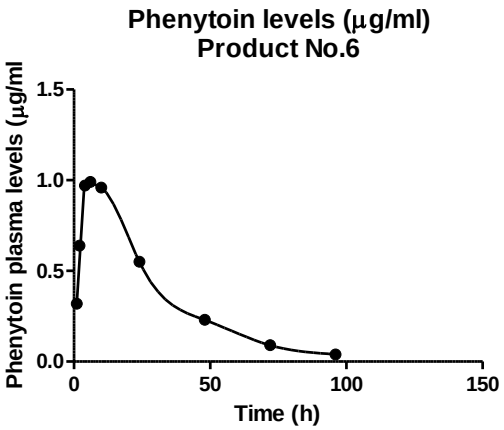

Figure 6: Observed plasma concentration time profile of phenytoin and the description of the observed profile with the developed model of the dynamic system describing the dynamic pharmacokinetic behavior of orally administered phenytoin [1].