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Model Based Description of the Pharmacokinetic Behavior of Pentobarbital in Fasted Male Volunteers after Oral Administration of 10 mg of Pentobarbital

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Abstract

The goal of the current study was to present a further example which showed a model based description of the pharmacokinetic behavior of pentobarbital in fasted male volunteers after oral administration of 10 mg pentobarbital. The current study is a companion piece of the earlier study by Smith et al.; therefore the data published in the study cited here were used. For modeling purposes, an advanced modeling method based on the theory of dynamic systems was employed. All mathematical models developed, more or less successfully described the data of healthy male volunteers after oral administration of capsules containing 50 mg of sodium pentobarbital. The modeling method used in the current study is universal and uniform. Therefore, it can be used to develop mathematical models not only in pharmacokinetics but also in several other scientific and practical fields. This modeling method could augment, or in future replace, a variety of different modeling methods traditionally used in pharmacokinetics.

Keywords: Pharmacokinetics; Mathematical model; Dynamic system

Introduction

Pentobarbital is a short-acting barbiturate. In the Western countries it is used as a sedative and axiolytic [1,2]. Except this, the intraperitoneal injection of a lethal dose of pentobarbital is quite commonly used to euthanize small animals in veterinary medicine [3]. Pharmacokinetics of pentobarbital in healthy male volunteers after intravenous and/or oral administration of pentobarbital was investigated in the previous study [1]. The current study is a companion piece of the previous study [1] published in January issue of the Journal of Pharmacokinetics and Biopharmaceutics [1]. Therefore the data published in the study cited here were used with the objective to present model based description of the pharmacokinetic behavior of pentobarbital in fasted male volunteers after oral administration of 10 mg pentobarbital. For modeling purposes an advanced mathematical modeling method based on the theory of dynamic systems was used [4-15]. Previous examples showing an advantageous use of the modeling method used in the current study can be found in the 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.

Materials and Method

As stated above, an advanced mathematical modeling method based on the theory of dynamic systems was used to develop mathematical models of the pharmacokinetic behavior of pentobarbital in healthy male volunteers enrolled in the study, and in the current study. The development of mathematical models of the pharmacokinetic behavior of pentobarbital was performed in the following steps:

In the first step, pharmacokinetic dynamic systems denoted by *H* were defined for all volunteers using the Laplace transform of mathematically described plasma concentration-time profiles of pentobarbital of volunteers, denoted by C(s), and considered as outputs of the pharmacokinetic dynamic systems defined and the Laplace transform of the mathematically described oral administration of pentobarbital to volunteers, denoted by *I* (s), and considered as an input to the pharmacokinetic dynamic systems defined.

At the beginning of the model development process, the following simplifying assumptions were made: a) initial conditions of all pharmacokinetic dynamic systems defined were zero; b) processes occurring in the body after the oral administration of pentobarbital were linear and time-invariant; c) concentrations of pentobarbital were the same throughout all subsystems of pharmacokinetic dynamic systems defined (where a subsystem was an integral part of a pharmacokinetic dynamic system defined); d) no barriers to the distribution and/or elimination process of pentobarbital existed. In the second step, the pharmacokinetic dynamic systems defined were used to mathematically represent static and dynamic properties [16-18] of the pharmacokinetic behavior of pentobarbital in volunteers.

In the third step, the transfer functions, denoted by *H(S),* of the pharmacokinetic dynamic systems defined were derived using the Laplace transforms of mathematically described plasma concentration-time profiles of pentobarbital, denoted by C(s), and considered as outputs of and the pharmacokinetic dynamic systems defined, and Laplace transform of the mathematically described oral administration of pentobarbital, denoted by I(S), and considered as an input to the pharmacokinetic dynamic systems defined (the lower case letter "***S***" denotes the complex Laplace variable), [5-15] and the following equation:

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

The pharmacokinetic dynamic systems defined were described with the transfer functions H(s). For modeling purposes, the computer program CTDB [10] and the polynomial transfer function model $H_M(s)$ [19] described by the following equation were used:

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

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On the right-hand-side of Equation. (2) is the Pade approximant [20,21] to the model transfer function $H_M(s)$,G is an estimator of the model parameter called a gain of a dynamic system, $a_1,\ldots a_n, b_1,\ldots b_m$ are additional model parameters, and n is the highest degree of the nominator polynomial, and m is the highest degree of the denominator polynomial, where n<m [5-15].

In the fourth step, the transfer functions H(s) were converted into equivalent frequency response functions, denoted by $F(i\omega_j)$ [21].

In the fifth step, the non-iterative method published previously [21] was used to determine mathematical models of a frequency response functions $F_M(i\omega_j)$ and point estimates of parameters of model frequency response functions $F_M(i\omega_j)$ 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 Eq. (2), in Eq. (3): n is the highest degree of the numerator polynomial of the model frequency response function $F_M(i\omega_j)$, m is the highest degree of the denominator polynomial of the model frequency response function $F_M(i\omega_j)$, $n \le m$, i is the imaginary unit, and ω is the angular frequency. In the fifth step, a model of a frequency response function $F_M(i\omega_j)$ was refined using the Monte-Carlo and the Gauss-Newton method in the time domain.

In the sixth step, the Akaike information criterion [22] was used to select the best models of the frequency response functions $F_M(i\omega_j)$ of all volunteers. In the final step, 95% confidence intervals of parameters of the best model of the frequency response functions $F_M(i\omega_j)$ were determined.

Results and Discussion

The best-fit polynomial model of $F_M(i\omega_j)$ of each volunteer was found using the Akaike Information Criterion. The structure of this model is described by the following equation:

$$F_M(i\omega_j) = G\frac{a_0 + a_1 i\omega_j}{1 + b_1 i\omega_j + b_2 i\omega_2 + b_3 i\omega_3 + b_4 i\omega_4}. \quad (4)$$

This model provided an adequate fit to the pentobarbital concentration data in all volunteers enrolled in the previous study [1], and in the current study. Estimates of the model parameters a_0, a_1,b_1, b_2, b_3, b_4 are in Table 1.

Volunteers L.N. and R.B. were arbitrarily chosen from all volunteers enrolled in the study[1] and in the current study, to illustrate modeling results obtained. Figure 1 depicts the observed plasma concentration time profile of pentobarbital and the description of the observed profile with the developed model of the pharmacokinetic dynamic system defined for volunteer L.N. Figure 2 illustrated the observed plasma concentration time profile of pentobarbital and the description of the observed profile with the developed model of the pharmacokinetic dynamic system, defined for volunteer R.B. Analogous results hold for all volunteers enrolled in the study [1] and in the current study (Table 2).

The pharmacokinetic dynamic systems used in the current study are mathematical objects, without any physiological relevance. They were used to model static and dynamic aspects of the pharmacokinetic behavior of pentobarbital [16-18] in the healthy volunteers enrolled in the study [1] and in the current study. The modeling method used in the current study has been described in detail in the previous studies [5-15], authored or co-authored by the author of the current study.

Model parameters	Estimates of model parameters	(95% CI)
G (min.ml^{-1})	0.0781	0.006 to 0.012
a_0 (-)	0.99	0.81 to 1.02
b_1 (min)	59.15	48.12 to 62.38
b_1 (min)	461.88	460.73 to 472.02
b_2 (min^2)	6033.61	6028.59 to 6040.33
b_4 (min^3)	3678275.74	3678271.05 to 3678280.33
b_4 (min^4)	48394155.81	29194567.21 to 62314574.21

Table 1: Parameters of the forth-order model of the dynamic systems describing the pharmacokinetic behavior of orally administered pentobarbital to volunteers enrolled in the study by Smith et al. and in the current study.

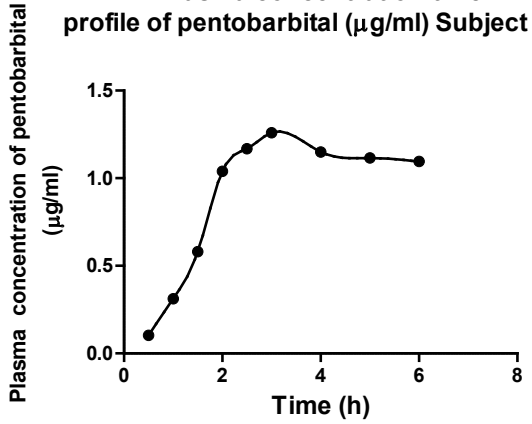

Figure 1: Observed plasma concentration time profile of pentobarbital and the description of the observed profile with the developed model of the dynamic system representing the static and dynamic properties of the pharmacokinetic behavior of orally administered pentobarbital in volunteer ln.

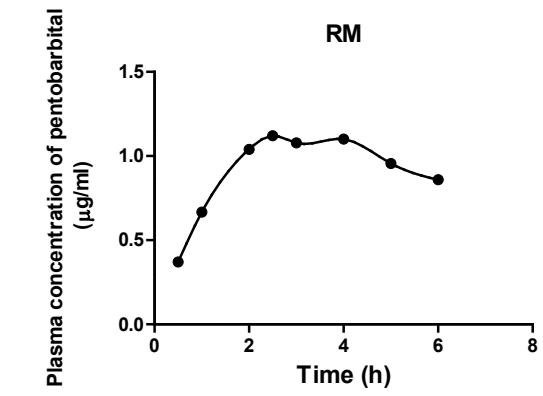

Figure 2: Observed plasma concentration time profile of pentobarbital and the description of the observed profile with the developed model of the dynamic system representing the static and dynamic properties of the pharmacokinetic behavior of orally administered pentobarbital in volunteer rm.

Pharmacokinetic variables	Estimates of pharmacokinetic variables
C_{max} (μg/ml)	1.26 ± 0.08*
t_{max} (hour)	3 ± 0.91
The half-time of pentobarbital $t_{1/2}$ (hour)	1.5 ± 0.4
Clearance of pentobarbital (ml/min)	12.8 ± 1.3

*standard deviation maximal pentobarbital concentration
C_{max} - maximal pentobarbital concentration in plasma
t_{max}- time to reach maximal pentobarbital concentration in plasma

Table 2: Model-based estimates of potentially important pharmacokinetic variables of orally administered pentobarbital to volunteers enrolled in the study by Smith et al. and in the current study.

Analogously to previous studies cited above, the development of a mathematical model of each pharmacokinetic dynamic system was based on the known input and output of a pharmacokinetic dynamic system, in the current study. In general, if a dynamic system is modeled using a transfer function model; as it was the case in the current study (see Equation. 2), then the accuracy of the model highly depends on the degrees of the polynomials of the transfer function model used to fit the data, see *e.g.* the following studies [5-15], and references therein.

The parameter gain is also called a gain coefficient, or a gain factor. It is a proportional value that shows a relationship between magnitudes of an input of a dynamic system to a magnitude of an output of 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 magnitudes of an output to a magnitude of an input of to a dynamic system in the steady state.

The exact meaning of a parameter gain depends on the nature of an investigated pharmacokinetic dynamic system; for example full-text articles available free of charge at: http://www.uef.sav.sk/advanced.htm.

The non-iterative method introduced in the study [20] and used in the current study provides quick identification of an optimal structure of a model frequency response. It is a great advantage of this method, because this significantly speeds up the development of a frequency response model.

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 $H_M(s)$ (see Equation. (2)) is a complex Laplace variable, while the angular frequency "ω" in the model frequency response function $F_M(i\omega_j)$ in Equation. (4) is a real variable, what is suitable for mathematical modeling in time domain.

The linear mathematical models developed in the current study more or less sufficiently approximated static and dynamic aspects [16-18] of the pharmacokinetic behavior of pentobarbital in all volunteers enrolled in the study [1], and in the current study.

The current study showed again 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 modeling is 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 dynamic systems investigated.

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 and/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 represented resulting plasma (or blood) concentration-time profile of a drug administered. See for example the full text articles published in peer-reviewed journals 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 [8]. Moreover, the methods considered here can be used for safe and cost-effective individualization of dosing of a drug or a substance, for example using computer-controlled infusion pumps. This is very important, for example for an administration of a clotting factor to a hemophilia patient, as exemplified in the simulation study [8].

The transfer function model, here denoted as $H_M(s)$ and the frequency response function model $F_M(i\omega_j)$ have been implemented in the computer program CTDB [10]. A demo version of the program CTDB is available at: http://www.uef.sav.sk/advanced.htm.

The advantages of the model and modeling method used in the current study are evident here: The models developed overcome one of the well-known limitations of compartmental models: For the development and use of the models considered here, an assumption of well-mixed spaces in the body (in principle unrealistic) is not necessary. The basic structure of the models developed in the current study is broadly applicable, and can be used 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 of the pharmacokinetic behavior of a drug in a human or an animal body. Transfer functions of dynamic systems are not unknown in pharmacokinetics [23-25]. In pharmacokinetics, transfer functions are usually called disposition functions [26].

The modeling method used in the current study is universal and uniform. Therefore, it can be used to develop mathematical models not only in pharmacokinetics but also in several other scientific and practical fields. The modeling method considered here can augment, or in future replace, a variety of different modeling method used in pharmacokinetics.

Conclusion

The models developed and used in the current study successfully described the pharmacokinetic behavior of pentobarbital after an oral administration to healthy volunteers enrolled in the previous study [1] and in the current study. The modeling method used in the current study is universal, and thus it can be applied to a broad range of dynamic systems not only in the field of pharmacokinetics but also in many other scientific and/or practical fields. The current study again showed that mathematical and computational tools from the theory of dynamic systems can be advantageously used in mathematical modeling in pharmacokinetics. To see the previous examples illustrating the

successful use of the modeling method employed in the current study please visits the author's web page (an English version): 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 several previous COST program actions. This work of the author in several international projects led to the preparation of several studies published previously and the current 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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