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RESEARCH ARTICLE

FURTHER WORKED OUT EXAMPLES THAT ILLUSTRATED THE SUCCESSFUL USE OF AN ADVANCED MATHEMATICAL MODELING METHOD BASED ON THE THEORY OF DYNAMIC SYSTEMS IN PHARMACOKINETICS

Ďurišová M

Department of Pharmacology of Inflammation, Institute of Experimental Pharmacology and Toxicology, Slovak Academy of Sciences Bratislava, Slovak Republic

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ABSTRACT

Background: Modeling tools from the theory of dynamic systems are not commonly used in pharmac evaluations.
Objective: Therefore, the objective of the current study was to show again that a modeling method employi from the theory of dynamic systems can be advantageously used for mathematical modeling in pharmacol Two examples were given: an example with single dose administration of indomethacin and an example wit dose administration of methotrexate.
Methods: An advanced modeling method employing computational and modeling tools from the th dynamic systems was used, see the following study: http://www.uef.sav.sk/advanced_files/ref-19.pdf
Results: The determined model-based estimates of the main pharmacokinetic parameters of indomethacin v half-life of elimination were: 4.600 ± 0.080 [hr], clearance: 0.045±0.009 [l/kg/hr]. The metabolic methotrexate and 7-hydroxymethotrexate was approximately constant, the mean time of the formatio hydroxymethotrexate from methotrexate increased, and the rate of the formation of 7-hydroxymeth decreased, during the first three months of the treatment of the patients with psoriasis with methotrexate.
Conclusion: The modeling method used can be employed to model the pharmacokinetics of any drug; w pharmacokinetic behavior of a drug is a linear process.

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INTRODUCTION

Mathematical tools from the theory of dynamic systems (26) are not traditionally used for modeling purposes in pharmacokinetics. However, these tools are usually used for theoretical purposes, except for a convolution integral which is used in convolution and/or deconvolution computations. The current study attempted to contribute to bridging the gap between theory and practice in pharmacokinetics. Therefore, it showed that a method based on the theory of dynamic systems (or in other word a modeling method employing computational and modeling tools from the theory of dynamic systems) can be advantageously used in mathematical modeling in pharmacokinetics.

The previous examples showing similar results to those obtained in the current study can be found in the full texts of research articles downloadable for free from the author's Web page: http://www.uef.sav.sk/advanced.htm.

Two pharmacokinetic examples were given in the current study: an example with a single dose administration of indomethacin to a human volunteer (4) and an example with a single dose administration of methotrexate to a patient with psoriasis (3).

The first pharmacokinetic example illustrated the development of a mathematical model of the pharmacokinetic behavior of the orally administered indomethacin to a healthy human volunteer, using the data from the study by: Cole *et al.* (1992) "Targeting drugs to the enterohepatic circulation: A potential drug delivery system designed to enhance the bioavailability of indomethacin. Int. J. Pharmaceut. 80: 63-73" (4). The second pharmacokinetic example illustrated the investigation of the time dependent formation of 7-hydroxymethotrexate (7OH-MTX) from methotrexate (MTX) in a patient treated with MTX for psoriasis. The data used for investigations were kindly supplied by the authors of the study: Chládek *et.al.* "Pharmacokinetics of low doses of methotrexate in patients with psoriasis over the early period of treatment". Eur. Drug Metab. Pharmacol. (1998) 53: 437-444 (3). The models developed successfully described the pharmacokinetic behavior of administered drugs in both examples. A few introductory articles, authored and/or co-authored by the author of the current study, have been published, with the aim to

Corresponding author:* **Ďurišová M
Department of Pharmacology of Inflammation, Institute of Experimental Pharmacology and Toxicology, Slovak Academy of Sciences Bratislava, Slovak Republic

show the successful use of methods employing computational and mathematical tools from the theory of dynamic systems can be used advantageously in mathematical modeling in pharmacokinetics, see *e.g.* the following studies (9-22), and references therein.

The main goal of the current study was to show again the advantageous use of the method considered here in mathematical modeling in pharmacokinetics, by presenting other two pharmacokinetic examples. The previous examples showing results similar to those obtained in the current study were presented in detail in the articles cited above, and/or they can be found in the full texts of research articles downloadable for free from the author's web page: http://www.uef.sav.sk/advanced.htm.

The first pharmacokinetic example illustrated the development of a mathematical model of the pharmacokinetic behavior of the orally administered indomethacin (non-steroidal anti-inflammatory drug) to a healthy human volunteer (4); The second pharmacokinetic example, illustrated a computational investigation of the time dependent formation of 7-hydroxymethotrexate (7OH-MTX) from methotrexate (MTX) in a patient treated with MTX for psoriasis (3). The data kindly supplied by the authors of the last-cited study and the mathematical modeling method developed by Dedík (9-22) were used. The models developed, more or less successfully fitted the experimental data in both examples.

Computational investigations of dynamic processes are most commonly performed employing differential equations in the time domain, or employing rather complicated methods in the complex domain, see *e.g.* the studies cited above and references therein. Mathematical modeling methods based on the theory of dynamic systems, (or in other words mathematical modeling methods that employ computational and modeling tools from the theory of dynamic systems) are methodologically rigorous and technically efficient. Therefore, they can be used for analyses of experimental data in several fields of science and engineering, including pharmacokinetics. Two pharmacokinetic examples were given in the current study.

Examples

The following simplifying assumptions were made with respect to the drug administered in both examples: 1) disposition of the drug was the result of repetitive possesses of the drug around the circulation (5); 2) the drug was uniformly distributed throughout the body; 3) the drug was not bound to serum proteins; 4) the disposition of the drug in plasma and/or in whole blood was linear and time invariant (23).

The first example

In the study by Cole *et al.* (4), an effect of exogenous added bile acids on bioavailability of indomethacin was investigated in healthy human volunteers, and pharmacokinetic evaluations were performed. However, no mathematical models of the pharmacokinetic behavior of indomethacin were developed. Therefore, a mathematical model of the pharmacokinetic behavior of indomethacin was developed, using the data published in the study (4), and the modeling procedure developed by Dedik (9-22). The modeling procedure involved the following successive steps:

In the first step, an ADME related dynamic system (thereafter, only the dynamic system *H*) was defined by using its transfer function (9-22), (denoted by *H(s)*) in the Laplace domain, where s is the Laplace variable:

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

It is apparent, looking at Eq. (1), that the profile *C(s)* was used as the output of the dynamic system *H* and the profile *I(s)* was used as the input into the dynamic system *H*. As seen in Eq. (1), the transfer function *H(s)* was derived by relating the Laplace transform of the plasma concentration-time profile of indomethacin *C(s)* to the Laplace transform of the indomethacin input into the body *I(s)*. The dynamic system *H* was used, as a powerful working tool, to mathematically describe both static and dynamic phenomena (31,27) connected with the pharmacokinetic behavior of indomethacin in the body. ADME is an acronym frequently used in pharmacokinetic texts. It is created from the first letter of each of the following words: absorption, distribution, metabolism, and excretion, of an administered drug.

In the second step, a mathematical model of the dynamic system *H* was developed, by using the model transfer function $H_M(s)$ described by Eq. (2):

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

On the right-hand-side of Eq. (2) is the Padé approximant of the function $H_M(s)$ of the order (n, m) (2-25), G is an estimator of the model parameter traditionally called a gain of a dynamic system (here, of the dynamic system *H*), $a_1, \cdots a_n$, $b_1, \cdots b_m$ are additional model parameters, n is the highest degree of the numerator polynomial, and m is the highest degree of the denominator polynomial, where $n<m$, see *e.g.* the following studies (9-22) and references therein.

In the third step, the model transfer function $H_M(s)$ was converted into the equivalent model frequency response function (denoted by $F_M(i\omega_j)$) in the frequency domain; see *e.g.* the studies cited above. Thereafter, the non-iterative previously published method (25) was used to determine the model frequency response function $F_M(i\omega_j)$ and also point estimates of the parameters of the model frequency response function $F_M(i\omega_j)$ in the frequency domain. The model

frequency response function $F_M(i\omega_j)$ used in the current study is described by the following equation:

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

The meaning of the symbols in Eq. (3) is the same as that in Eq. (2).

In the fifth step, the best model frequency response function $F_M(i\omega_j)$ was selected on the basis of the lowest value of the modified Akaike information criterion. The Akaike information criterion was modified, according to Dedík and Ďurišová (9), in order to obtain the Akaike information criterion usable in the complex domain (1).

In the last step, interval estimates of the parameters of the AIC-optimal models $F_M(i\omega_j)$ were determined by using the Gauss-Newton method in the time domain; see *e.g.* the following studies (9-10) and references therein. On the basis of the model developed, the following pharmacokinetic parameters of indomethacin were derived: elimination half-life, volume of distribution, plasma clearance. Finally, the total amount of indomethacin eliminated was estimated.

RESULTS

The first example

The plasma concentration-time profile of indomethacin was shown in Figure 1 (points). The mathematical model developed was shown in the same figure (line). As seen, the mathematical model developed more or less successfully fitted the observed plasma concentration-time profile of indomethacin. The pharmacokinetic parameters determined were listed in Table 1. An estimate of the total amount of indomethacin eliminated by bile was 7 % of the given dose of indomethacin. Similar results were obtained for all subjects investigated (all results obtained were not shown in the current study).

Table 1 Main pharmacokinetic parameters of indomethacin

Main pharmacokinetic parameters	Estimates of main pharmacokinetic parameters
Half-life of elimination	4.600 ± 0.080 [hr]
Volume of distribution	0.340 ±0.0100[l/kg]
Plasma clearance	0.045±0.009 [l/kg/hr]
Time to reach the maximum indomethacin concentration in plasma	2±0.01 [hr]
The maximum indomethacin concentration in plasma	3.95 [μgr/ml]

The second example

The chemotherapeutic agent methotrexate (MTX) is widely used in tumor therapy for different forms of leukemia, and for the therapy of arthritis and psoriasis. 7-hydroxymethotrexate (7OH-MTX) is the major metabolite of methotrexate (MTX).

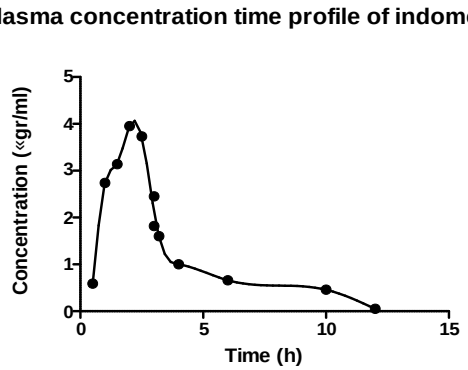

Figure 1 Plasma concentration-time profile of indomethacin (points) and the developed mathematical model of the pharmacokinetic behavior of indomethacin in the subject investigated (line).

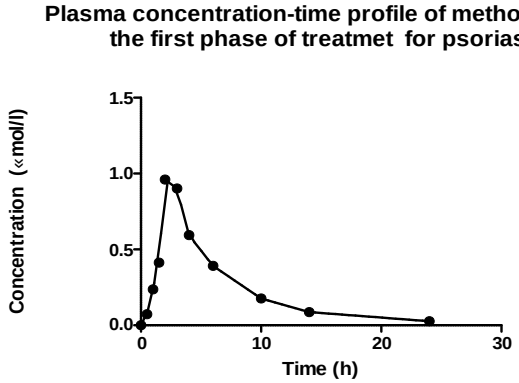

Figure 2 Plasma concentration-time profile of methotrexate of Patient No.1 during the first phase of treatment for psoriasis.

In the study (3), MTX was administered to patients with psoriasis in an oral dose of 15 mg once per week. In an initial pilot study (11), co-authored by the author of the current study, a method was developed and successfully applied to model the formation of 7OH-MTX from MTX in a patient treated with MTX for psoriasis (3,11). The current study is a continuation of the earlier studies (3,11). Therefore, the goal of the second example was to computationally investigate the time dependent formation of 7OH-MTX from MTX in a patient undergoing treatment with MTX for psoriasis during the early phase (3months) after the start of the therapy.

Table 2 Main characteristics of methotrexate metabolic process

	First MTX dose	Fifth MTX dose	Thirteenth MTX dose
Metabolic ratio	0.67±0.08*	0.58±0.05	0.59±0.09
Mean formation time of 7OH-MTX from MTX (h)	9.35±1.79	9.90±1.02	15.59±2.214

*SD
MTX – methotrexate
7OH-MTX7-hydroxymethotrexate

An investigation of the time dependent formation of 7OH-MTX in a patient treated with MTX for psoriasis was performed using data kindly provided by the authors of the study by Chládek *et al.* (3). For the modeling purposes the method developed by Dedík (9-10) was used. The modeling procedure used was described in the previous section.

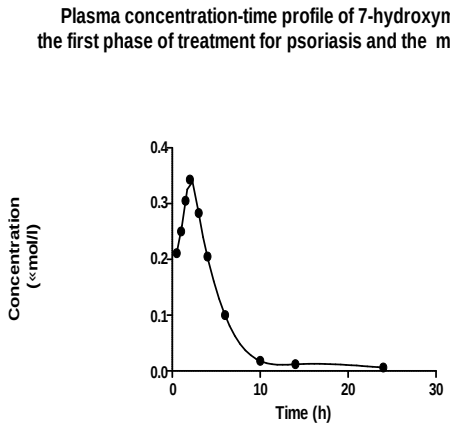

Figure 3 Plasma concentration-time profile of 7-hydroxymethotrexate of Patient No.1 during the first phase of treatment for psoriasis.

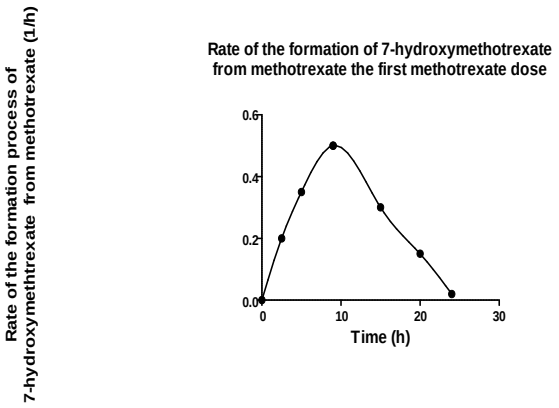

Figure 3a Rate of the formation of 7-hydroxymethotrexate from methotrexate after the first methotrexate dose.

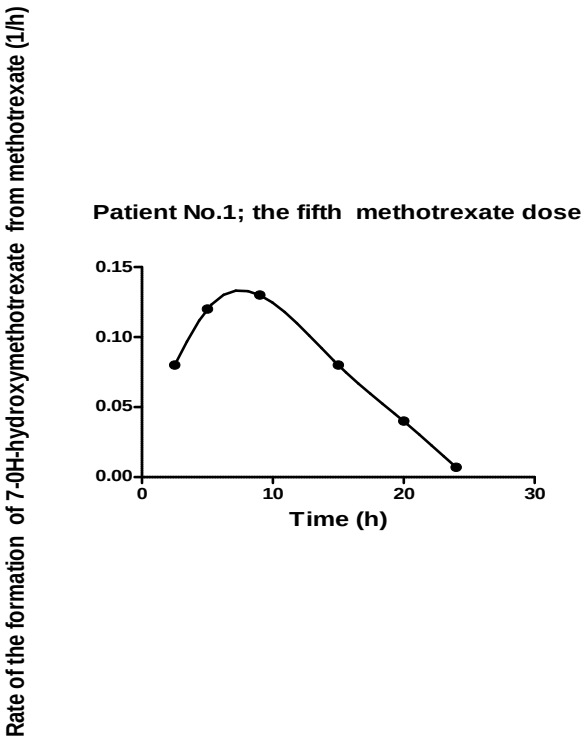

Figure 3b Rate of the formation of 7-hydroxymethotrexate from methotrexate after the fifth methotrexate dose.

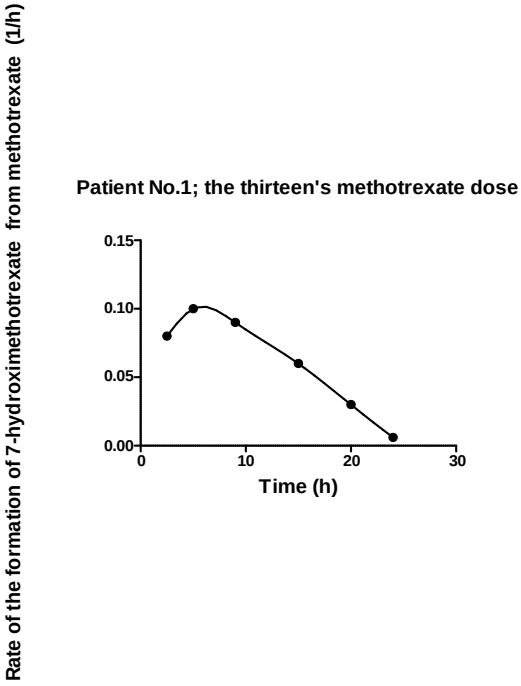

Figure 3c Rate of the formation of 7-hydroximethotrexate from methotrexate after the thirteen's methotrexate dose.

The investigation started with the definition of a patient-specific dynamic system in the Laplace domain. In thereafter, the patient-specific dynamic system was simply called the dynamic system H. Dynamic system H was defined in such a way that the Laplace transform of the plasma concentration-time profile of MTX was used as the input into dynamic system *H*, and the Laplace transform of the plasma concentration-time profile of 7OH-MTX was used as the output of the dynamic system *H*, see *e.g.* the following studies [11-10], and references therein. The dynamic system H was described with its transfer function (denoted by $H(s)$) in the Laplace domain (9-22). The transfer function $H(s)$ was derived, using the Laplace transform of the plasma concentration-time profile of 7OH-MTX (denoted by $C_{7OH-MTX}(s)$), as an output of the dynamic system *H*, and the Laplace transform of the plasma concentration-time profile of MTX (denoted by $C_{MTX}(s)$), as an input into the dynamic system *H*, see the following equation:

$$H(s) = \frac{C_{7OH-MTX}(s)}{C_{MTX}(s)}. \quad (5)$$

A model of the dynamic system H was developed using the method described previously (9-22). Based on the models developed, the following pharmacokinetic parameters were derived: the metabolic ratio of MTX to 7OH-MTX, the rate of the formation of 7OH-MTX from MTX, and the mean formation time of 7OH-MTX from MTX.

The results obtained for the patient investigated were presented in Figure 2 and Figure 3, and in Table 2. Figure 2 showed the

observed plasma concentration-time profile of MTX. Figure 3 showed observed plasma concentration-time profile of 7OH-MTX and the developed model of the patient's dynamic system *H*. Figures 3a, 3b, and 3c showed the formation rate of 7OH-MTX from MTX after the first, fifth, and thirteenth MTX dose, respectively. As seen in Figures 3a, 3b, and 3c, the maximum rate of the formation of 7OH-MTX from MTX decreased from the value of about 0.5 (1/h) after the first MTX to the value of about 0.1 (1/h) after the thirteen's MTX dose.

The determined characteristics of methotrexate metabolic process: the metabolic ratio, mean time of the formation of 7OH-MTX from MTX and rate of the formation of 7OH-MTX from MTX were listed in Table 2. It can be observed that metabolic ratios remained approximately constant at the level of about 0.6 after administration of the three doses of MTX. However, the mean time of the formation of 7OH-MTX from MTX increased from the value of about 9 h after the first MTX dose to the value of about 15 h after thirteenth MTX dose. Similar results were obtained for all subjects enrolled in the study (3) (all results obtained were not shown in the current study).

DISCUSSION

The most important conceptions rising from the current study were as follows:

In general, a parameter gain of a dynamic system is a proportional value that shows the relationship between a magnitude of an input to a magnitude of an output of a dynamic system at steady state. The practical meaning of a parameter gain depends on the nature of the dynamic system under study (9-22). For example: 1) the reciprocal value of the parameter gain is an estimate indomethacin clearance in the first pharmacokinetic example; 2) the parameter gain determines the metabolic ratio in the second example (11,22).

Frequency response functions are complex functions, including both real and imaginary components, therefore, the modeling methods used to model frequency response functions are computationally intensive, and modeling is performed in the complex domain. Moreover, the methods considered here require at least partial knowledge of the theory of dynamic system, and an abstract way of thinking about a dynamic system under study.

The principal difference between traditional pharmacokinetic modeling methods and modeling methods that use of mathematical and computational tools from the theory of dynamic systems, lies in the following: the former methods are based on modeling plasma (or blood) concentration versus time profiles of drugs, however, the latter methods are based on modeling a relationship between a mathematically described drug administration and a mathematically described resulting plasma(or blood) concentration-time profile of the drug administered (10-16). See, *e.g.* the full texts of research articles downloadable for free from the author's web page: 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 drug administration aimed at achieving and then maintaining required drug concentration–time profiles in patients, and/or for safe and cost-effective individualization of drug dosing. This is very important, for example in an administration of a clotting factor to hemophilia patients [15].

Unique properties of the model and modeling method used in the current study are evident here: The models developed overcome one of the typical limitations of compartmental models: For the development and use of the models presented here, an assumption of well-mixed spaces in the body is not necessary. On using the modeling methods considered here, no requirement of a specific model structure (in general unknown) is necessary and no abstract assumption of well-mixed compartments. The model structure used in the Laplace domain and the model structure used in the frequency domain are general (see Eq. (2) and Eq. (3). Therefore they can be employed in mathematical modeling various dynamic systems in the field of pharmacokinetics and in many other fields. From a point of view of pharmacokinetic community, an advantage of the models developed and used in the current study is that the models considered here emphasize dynamic and static aspects of the pharmacokinetic behavior of a drug in a human body. The modeling method used in the current can be easily generalized and can be further employed in several studies. The current study was written in a language that readers not familiar with the theory of dynamic systems will easily understand.

Concluding remark

One of founders and internationally known leader in pharmacokinetics John G. Wagner in his work [29] wrote: A modern view of pharmacokinetics must include both linear and nonlinear systems. The current study is in line with the study cited above. Moreover, in the current study, the author wanted to show that an integration of pharmacokinetic and bioengineering approaches is a good and efficient way to study various processes in pharmacokinetics. The reason for this is that such an integration combines mathematical rigor with biological insight.

Note

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About the author

The author is affiliated with the Institute of Experimental Pharmacology and Toxicology at the Slovak Academy of

Sciences Bratislava, Slovak Republic. The main scientific interest of the author is mathematical modeling various biomedical systems. More information about the modeling methods used by the author of the current study and their application in pharmacokinetics can be found at: www.uef.sav.sk/durisova.htm. During the preparation of the current study, the author of the current study was a member of the Management Committee of the COST Action BM1204 entitled: An integrated European platform for pancreas cancer research: from basic science to clinical and public health interventions for a rare disease. This was the reason, why an example with methotrexate was given in the current study.

Conflict of interest

The author has reported no potential conflicts of interest relevant to this study.

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