Durisova, Clin Exp Pharmacol 2016, 6:3
DOI: 10.4172/2161-1459.1000205

Journal of
Clinical and Experimental Pharmacology

Research Article Open Access

Computational Investigation of Time Dependent Changes in the Formation of 7-Hydroxymethotrexate from Methotrexate in Patients Undergoing Treatment for Psoriasis with Methotrexate

Durisova M*

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

***Corresponding author:** Durisova M, Department of Pharmacology of Inflammation, Institute of Experimental Pharmacology and Toxicology, Slovak Academy of Sciences, Bratislava, Slovakia, Tel: (00421) 2 54775928; Fax: (00421) 2 54775928; E-mail: maria.durisova@savba.sk

Received date: November 17, 2015; **Accepted date:** April 28, 2016; **Published date:** May 02, 2016

Abstract

Objective: To investigate time dependent changes in the formation of 7-hydroxymethotrexate (7OH-MTX) from methotrexate (MTX) in patients undergoing treatment for psoriasis with MTX.

Method: This study is a companion piece of the study by Chladek et al. therefore the data from the study cited here was used. For modeling purposes a modeling method based on the theory of dynamic systems was employed.

Results: The metabolic ratios of MTX to 7OH-MTX in plasma were constant during the first three months of the treatment of the patients for psoriasis with MTX. However, the mean time of the formation of 7OH-MTX from MTX increased from the value of about 9.35 h in the first phase of treatment to the value of about 15.59 in the third phase of treatment. The rate of the formation of 7OH-MTX from MTX decreased from 0.51/h to 0.29 1/h during the same time interval.

Conclusions: All models developed; successfully described the data of all patients enrolled in the previous study by Chladek et al. the modeling method used is universal. Therefore, it can be used to develop mathematical models not only in pharmacokinetics but also in several other scientific and practical fields.

Keywords: Methotrexate; Oral administration; Mathematical model

Introduction

In current study, 7-hydroxymethotrexate (7OH-MTX) from methotrexate (MTX) was performed in the same time interval. Data kindly provided by the authors of the study were used. 7OH-MTX is the major metabolite of MTX [1-3]. In the study MTX was administered to patients with psoriasis in an oral dose of 15 mg once per week. In an initial pilot study [4], co-authored by the author of the current study, an advanced modeling method was developed and successfully used to model the formation of 7OH-MTX from MTX. The current study is a sequel to the previous studies [1,4], therefore, combined models for MTX and 7OH-MTX were developed. The investigation started with the definition of patient-specific dynamic systems, denoted by H, in the Laplace domain [4-10]. Dynamic systems H were defined in such a way that the Laplace transforms of the plasma concentration-time profiles of MTX (Figure 1) were used as the inputs to dynamic systems H and the Laplace transforms of the plasma concentration-time profiles of 7OH-MTX (Figure 2) were used as the outputs of the dynamic systems H. In the following text, the patient-specific dynamic systems were simply called the dynamic systems H. The dynamic systems H were described with transfer functions denoted by $H(s)$ in the Laplace domain: $H(s) = \frac{C_{7OH-MTX}(s)}{C_{MTX}(s)}$ (1) In Equation (1), $C_{7OH\text{-}MTX}(s)$ is the Laplace transform of the plasma concentration-time profile of 7OH-MTX, $C_{MTX}(s)$ is the Laplace transform of the plasma concentration-time profile of MTX, and s is the complex Laplace variable. Models of the dynamic systems H were developed using the method described previously [4-10].

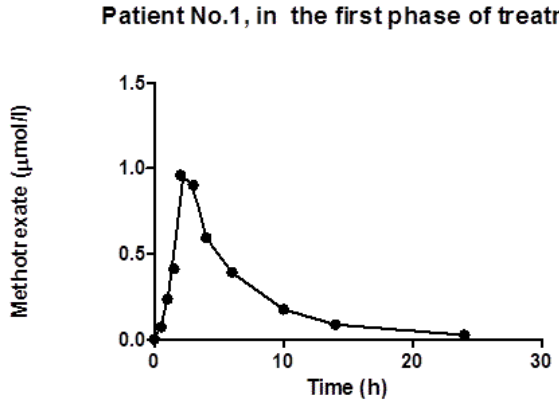

Figure 1: Observed plasma concentration-time profile of methotrexate.

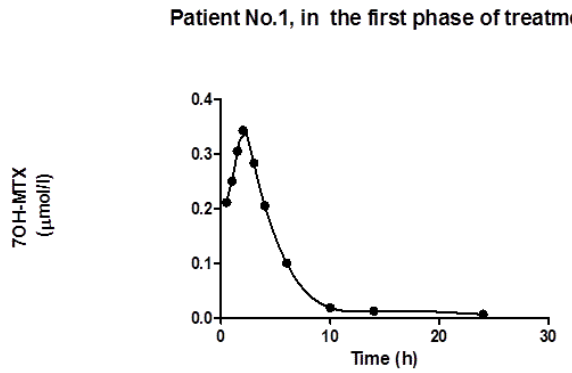

Figure 2: Observed plasma concentration-time profile of 7-hydroymethotrexate (7-OH-MTX) and the description of the observed profile with the developed model of the patient's dynamic system.

The models developed were used: 1) to determine: metabolic ratio, rate of the formation of 7OH-MTX from MTX, and mean formation time of 7OH-MTX from MTX; 2) to investigate time dependent changes in the formation of 7OH-MTX from methotrexate MTX in patients undergoing treatment for psoriasis with MTX.

Results and Discussion

Patient No. 1 was randomly selected among all patients enrolled in the study [1], to show the results obtained. The results revealed that during the first three months of the treatment of the patients for psoriasis with MTX: 1) the metabolic ratios were approximately constant; 2) the mean time of the formation of 7OH-MTX from MTX increased from the value of about 9.35 ± 1.79 h to the value of about 15.59 ± 2.22 h; 3) the rate of the formation of 7OH-MTX from MTX decreased from the value of about 0.5 1/h to the value of about 0.29 1/h, Table 1.

	The first phase of treatment	The second phase of treatment	The third phase of treatment
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 ± 2.22
*SD; MTX – Methotrexate; 7OH-MTX -7-hydroxymethotrexate			

Table 1: Metabolic ratio for psoriasis treatment.

Figure 2 shows observed plasma concentration-time profile of 7OH-MTX and the description of the observed profile with the developed model of the patient's dynamic system H. As it can be seen in Figure 2, the model developed more or less successfully described observed plasma concentration-time profile of 7OH-MTX.

Figures 3a-3c shows the rate of the formation of 7OH-MTX from MTX in the first, second, and third phase of treatment, respectively. As seen in Figures 3a-3c, the maximum rate of the formation of 7OH-MTX from MTX decreased from the value of about 0.51 (1/h) in the first phase of treatment to the value of about 0.29 (1/h) in the third phase of treatment. The determined quantities: metabolic ratios of MTX to 7OH-MTX, mean time of the formation of 7OH-MTX from MTX and rates of the formation of 7OH-MTX from MTX are listed in Table 1. It can be observed that metabolic ratios remained approximately constant between the first and third phase of treatment. However, the mean time of the formation of 7OH-MTX from MTX increased from around 9.35 h in first phase of treatment to around 15.9 h in the third phase of treatment. The mean formation time of 7OH-MTX from MTX increased from the value of about 9.35 ± 1.79 h, in the first phase of treatment to the value of about 15.59 ± 2.22 h in the third phase of treatment Figures 3a-3c show decrease in the rate of the formation of 7OH-MTX from MTX from the maximum value of about 0.52 ± 0.09 1/h after the first MTX dose to the maximum value of about 0.29 ± 0.07 1/h after the thirteenth MTX dose. Analogous results hold for all patients enrolled in the study [1] and in the current study.

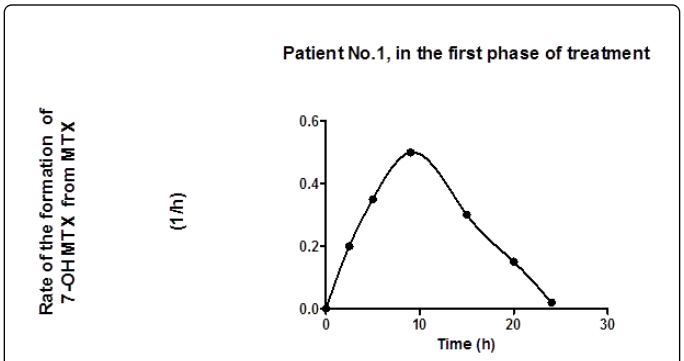

Figure 3a: Rate of the formation of 7-hydroxymethotrexate (7OH-MTX) from methotrexate (MTX).

The dynamic systems used in the current study were mathematical objects, which have no physiological significance. They were merely working tools, used: 1) to mathematically represent static and dynamic properties of the formation of 7OH-MTX from MTX in all patients; 2) to describe how one state of the formation of 7OH-MTX from MTX developed into another state over the course of time; 3) to mathematically represent dynamic processes associated with methotrexate metabolism in all patients with psoriasis. The mathematical modeling approach used in the current study has been described in detail in the previous studies authored and/or co-authored by the author of the current study; see for example the following studies [4-10].

These facts were taken into account for the definition of the dynamic systems. Transfer functions, also used in the current study, are fundamental equations of the theory of dynamic systems. They are not unknown in pharmacokinetics, where transfer functions are usually called disposition functions [11,12].

Even though the metabolic pathways of MTX have been well elucidated and several studies described the development of mathematical models of drug metabolism, see for example the following studies [2,13-18], little is known about time dependent changes in the formation of 7OH-MTX from MTX in patients undergoing treatment for psoriasis with MTX. Bridging this gap appears to be a big step. This was the reason why a computational investigation of time dependent changes in the formation of 7OH-

MTX from MTX in patients undergoing treatment for psoriasis with MTX was performed in the current study.

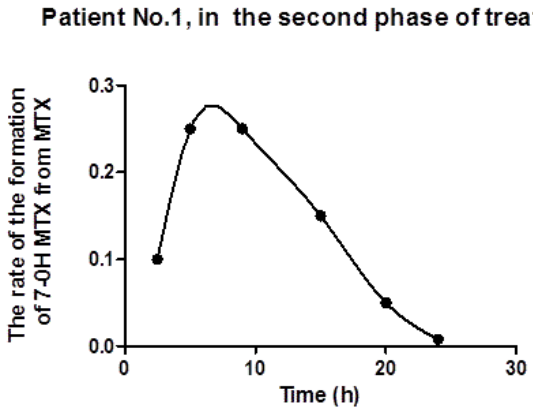

Figure 3b: Rate of the formation of 7-hydroxymethotrexate (7OH-MTX) from methotrexate (MTX).

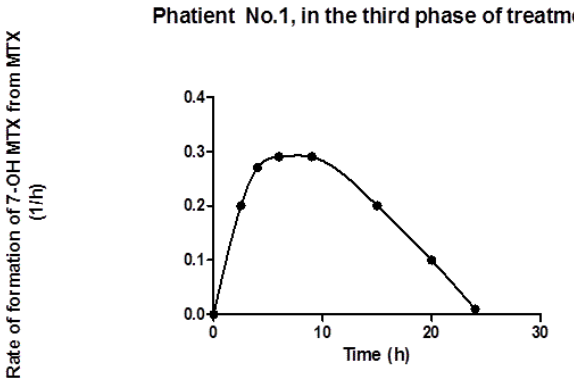

Figure 3c: Rate of the formation of 7-hydroxymethotrexate (7OH-MTX) from (MTX).

On purpose, mathematical details of the method used were not included. Instead, readers interested in the mathematical details of the method used were referred to literature.

The models developed in the current study did not attempt to address all aspects of the formation of 7OH-MTX from MTX in patients treated for psoriasis, because no mathematical model can exactly describe such a complicated process as is a metabolic process. Therefore, further investigations in humans are required to identify un-modeled aspects of the formation of 7OH-MTX from MTX in the current study [19].

The theory of dynamic systems is a well-established theory which deals with analyses of dynamic systems. Disadvantages of modeling methods that use tools from the theory of dynamic systems are as follows: these methods seems to be quite computationally complex, equations used in these methods are formulated in terms of Laplace transforms, what gives rise to different problems for some users. The methods considered here require an appropriate theoretical framework; see e.g. full text articles, available without any charge at: http://www.uef.sav.sk/durisova.htm. However, the use of tools from the dynamic systems for modeling purposes offers the following advantages: no specific model structures are necessary, no abstract unrealistic assumptions of homogenous well-mixed body parts (in general unrealistic) are not necessary [20-22].

Computational and modeling tools from the theory of dynamic systems are not commonly used in pharmacokinetics. However, these tools can be employed advantageously in studies of drug metabolism, as exemplified in the previous study [23] and in the current study. More information about successful use of computational and modeling tools from the theory of dynamic system in pharmacokinetics can be found in several full-text articles which are available free of charge at the author's web page (an English version): http://www.uef.sav.sk/advanced.htm.

The current study again showed that mathematical and computational tools from the theory of dynamic systems can be advantageously used in pharmacokinetic modeling. Reasons for this are many, in particular: i) unlike traditional pharmacokinetic methods, methods based on the theory of dynamic systems exhibit the following desirable properties: 1) they do not require any prior hypothesis about specific model structures (in general unknown); ii) they do not require abstract assumptions of homogenous well-mixed contents of body parts (in general unrealistic).

Concluding remarks: Much work remains to be done for further development of the modeling method used in the current study, and the implementation of the modeling method used in user-friendly modeling software. Clinical significance of the results obtained in the current study with respect to the use of MTX in the treatment of different cancers must be verified by additional investigations. For this reason a full utilization of the results obtained lies far in the future.

The modeling method employed in the current study can be used to model any drug metabolized in the body; when drug disposition in the body is at least approximately linear and parent and metabolite blood concentration-time profiles are available.

The current study reaffirmed 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.

During the preparation of the current study, the author precipitated in the Action BM1204 of the COST-EU program entitled: An integrated European platform for pancreas cancer research: from basic science to clinical and public health interventions for a rare disease.

Acknowledgements

The author gratefully acknowledges the financial support from the Slovak Academy of Sciences in Bratislava, Slovak Republic. The author thanks reviewers for their helpful comments on an earlier draft of this article. The author also thanks the authors of the study Chladek et al. who provided the data used in the current study.

Conflict of Interest

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

References

1. Chladek J, Martinkova J, Simkova M, Vaneckova J, Koudelkova V, et al. (1998) Pharmacokinetics of low doses of methotrexate in patients with psoriasis over the early period of treatment. Eur Drug Metab Pharmacol 53: 437-444.
2. Pang KS (1985) A review of metabolite kinetics. J Pharmacokinet Biopharm 16: 633-662.
3. Newton PA, Blakley RL (1984) Hydeoxymethotrexate formation in human lymphoblastic cell line. Biochem Biophys Res Commun 122: 122-127.
4. Dedik L, Durisova M (2002) System approach to modeling metabolite formation from parent drug: A working example with methotrexate. Methods Find Exp Clin Pharmacol 24: 481-486.
5. Dedik L, Durisova M (1995) Building a structured model of a complex pharmacokinetic system with time delays. Bull Math Biol 57: 787-808.
6. Dedik L, Durisova M (1997) Modeling in frequency domain used for the assessment of in vivo dissolution profile. Pharm Res 14: 860-864.
7. Dedik L, Durisova M (2005) New mathematical methods in pharmacokinetic modeling. Basic Clin Pharmacol Toxicol 96: 335-342.
8. Durisova M (2014) A physiological view of mean residence times. Gen Physiol Biophys 33: 75-80.
9. Durisova M (2015) Mathematical models of the pharmacokinetic behavior of cefamandole in healthy adult volunteers after 10 min intravenous administration of cefamandole. Int J Drug Dev and Res 7: 31-34.
10. Durisova M (2015) Mathematical models of pharmacokinetic behavior of digoxin in five healthy subjects following rapid intravenous injection of 1 mg of digoxin. J Develop Drugs 4: 1-4.
11. Wessels JA, Huzinga TW, Guchelaar HJ (2008) Recent insights in the pharmacological actions of methotrexate in treatment of rheumatoid arthritis. Rheumatology 47: 249-255.
12. Shen S, O'Brien T, Yap LM, Prince HM, Mc Cormack CJ (2012) The use of methotrexate in dermatology: A review. Australas J Dermatol 53: 1-18.
13. Meade T, Cumming S, Hallab L, Spencer D, Howe G, et al. (2013) A preliminary investigation of cognitive function in rheumatoid arthritis on long-term methotrexate treatment. J Health Psychol 18: 1353-1359.
14. Popovic J (2004) Classical Michaelis-Menten and system theory approach to modeling metabolite formation kinetics. Eur J Drug Metab Pharmacokinet 29: 205-214.
15. Karol MD, Goodrich S (1988) Metabolite formation pharmacokinetics: Rate and extent of metabolite formation pharmacokinetics: Pharm Res 5: 347-351.
16. St-Pierre MV, Lee PL, Pang KS (1992) A comparative investigation of hepatic clearance models: Predictions of metabolite formation and elimination. J Pharmacokin Biopharm 20: 105-145.
17. Weiss M (1998) Analysis of metabolite formation pharmacokinetics after intravenous and oral administration of the parent drug using inverse Laplace transformation. Drug Metab Disp 26: 562-565.
18. Lindsey JK, Wang J, Jones B, Byrom WD, Hin ID (2000) Simultaneous modeling of flosequinan and its metabolite. Eur J Clin Pharmacol 55: 827-836.
19. Siegel RA (1986) Pharmacokinetic transfer functions and generalized clearances. J Pharmacokin Bio-Biopharm 14: 511-524.
20. Holz M, Fahr A (2001) Compartment modeling. Adv Drug Del Rev 48: 249-264.
21. Weiss M (1988) A general model of metabolite kinetics following intravenous and oral administration of parent drug. Biopharm Drug Dispos 9: 159-176.
22. Rescigno A (2010) Compartmental analysis and its manifold applications to pharmacokinetics. AAPS Journal 12: 61-72.
23. Gillespie WR, Veng-Pedersen P, Berg MJ, Schottelius DD (1986) Linear systems approach to the analysis of an drug removal process. Phennobarbital removal by oral activated charcoal. J Pharmacokin Biopharm 14: 19-28.