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A physiological view and structures of mean residence times

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Abstract. The author's previous theoretical study described the determination of a physiologically realistic structure of a mean residence time of an intravenously administered drug (Ďurišová 2012). This study continues previous work and the aim is to determine physiologically realistic structures of mean residence times of a drug administered either orally (MRT_{po}) or intramuscularly (MRT_{im}). The determinations are based on the following assumption: a cardiopulmonary, portal, portal-venous, hepatic-portal subsystem, and a subsystem that mathematically represents non-eliminating tissues can be considered to be most important in terms of their impact on MRT_{po} and MRT_{im}. If drug fate and disposition is a linear process, the used method allows developing mathematical models without any prior knowledge or hypothesis concerning drug fate and disposition. This is a great advantage of the method considered here when compared with compartment methods. The research presented in this study was aimed at contributing to the knowledge base of physiological origins of mean residence times.

Key words: Mean residence time — Pharmacokinetics — Circulatory model — Hepatic elimination

Abbreviations: ADME – absorption, distribution, metabolism, and elimination related dynamic system; MRT, mean residence time.

Introduction

A mean residence time (*MRT*) is one of the major parameters that are used for investigations in pharmacokinetic studies. However, to the best of the author's knowledge, physiologically realistic structures of *MRT* have not been published as yet, with the exception of the author's previous theoretical study (Ďurišová 2012). One explanation for this fact is probably that physiologically realistic structures of *MRT* cannot be determined with tools commonly used in pharmacokinetics. Therefore, tools from the theory of dynamic systems, (see e.g., Gajic and Lelic 1996; Gajic and Lim 2001), were employed to determine a physiologically realistic structure of *MRT* of a drug administered intravenously (MRT_{iv}) (Ďurišová 2012). This study describes the determinations of physiologically realistic structures of *MRT* of a drug administered either orally (MRT_{po}) or intramuscularly (MRT_{im}). The term ADME (absorption, distribution, metabolism, and elimination related dynamic system) was originally developed and used in the author's previous theoretical study. ADME related dynamic systems are abstract mathematical constructs, without any physiological relevance. ADME is a well-known acronym in pharmacokinetics (see e.g., Eddershaw et al. 2000). A design of an ADME related dynamic system is a simple procedure, it can be performed in the following way: a function approximating a drug input into the body is used as an input to an ADME related dynamic system, and a function approximating a response of the body to the drug input is used as an output of ADME related dynamic system (Ďurišová et al. 1995; Dedík and Ďurišová 1996; Ďurišová and Dedík 1997; Tvrdoňová et al. 2009). Thereafter, the ADME related dynamic systems are simply called "the dynamic systems".

It is well known that a dynamic process associated with drug fate and disposition is controlled by several dynamic mechanisms and influenced not only by diverse dynamic

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interactions between the drug administered and physiological environment but also by various factors (Chiou 1983; Verotta et al. 1991). Therefore, several studies described investigations of the dynamic process associated with drug fate and disposition with the aid of dynamic systems. The investigations were performed in the following way: (a) dynamic systems were defined, (b) optimal circulatory models of the dynamic systems were selected through the Akaike information criterion (Akaike 1974) and (c) parameters of the optimal models were estimated (Ďurišová et al. 1995; Ďurišová and Dedík 1997; Dedik et al. 2009).

The terminology used in the current theoretical study is commonly used in studies of dynamic systems. It is significantly different from the terminology commonly used in pharmacokinetic studies. The essential difference is that between the physiological nature of the information conveyed by a physiological system and the functional nature of the information conveyed by the dynamic systems used in the current theoretical study. In the current theoretical study, the dynamic systems are used as means to mathematically represent dynamic processes associated with drug fate and disposition (Weiss and Pang 1992; Xiao et al. 2012). Another difference is related to the use of the term „dynamic": In pharmacokinetics, the term „dynamic" is widely used in descriptions of drug actions (Zuideveld et al. 2002). In the current theoretical study the term "dynamic" is used to indicate continuous changes in processes associated with drug fate and disposition. The differences in terminology outlined above do not have any consequence on pharmacokinetics.

Methods

The physiologically realistic structures of MRT_{po} and MRT_{im} are determined using two theoretical examples, two ADME related dynamic systems, and the same method as that previously described (Ďurišová 2012). The method considered here can be briefly described as follows: The dynamic process associated with drug fate and disposition was regarded as a result of repetitive passes of the drug around the blood circulation (Cutler 1979). The determination of a physiologically realistic structure of MRT_{iv} was performed in the following manner: In the first step, a theoretical example was created for illustrative purposes. In the second step a dynamic system was defined that mathematically represented the dynamic process associated with drug fate and disposition after the intravenous drug administration. In the third step, a circulatory model of the system defined was developed (Bassingthwaighte and Ackerman 1967; Weiss and Föester 1979). In the last step, a circulatory model developed and the method previously published (Ďurišová et al. 1995) were used to determine a physiologically realistic structure of MRT_{iv}.

In this study, the determinations of the physiologically realistic structures of MRT_{po} and MRT_{im} are performed analogously to that previously described (Ďurišová 2012). The determinations consist of these steps: In the first step, the following assumptions were made: (a) drug fate and disposition was a linear dynamic process, (b) the drug was mainly eliminated by the biliary route (c) the drug was not bound to plasma proteins or tissues, (d) the drug was orally administered in a tablet which was rapidly dissolved in gastrointestinal fluid, (e) the dissolved drug was rapidly emptied *via* the bile into the small intestine and is then reabsorbed into the blood circulation, (f) no barriers to the distribution (or elimination) of the drug existed. In the second step, the dynamic systems H_{po} and H_{im} were defined, that mathematically represented the dynamic processes associated with drug fate and disposition after an oral and intramuscular administration, respectively. In the third step, circulatory models of the dynamic systems H_{po} and H_{im} were developed, and the transfer functions $H_{po}(s)$ and $H_{im}(s)$ of the systems H_{po} and H_{im} were determined. In the fourth step MRT_{po} and MRT_{im} were described by the following general equations

$$MRT_{po} = \frac{\lim_{s\to 0} \frac{dH_{po}(s)}{ds}}{\lim_{s\to 0} H_{po}(s)} \quad (1)$$

$$MRT_{im} = \frac{\lim_{s\to 0} \frac{dH_{im}(s)}{ds}}{\lim_{s\to 0} H_{im}(s)} \quad (2)$$

in the Laplace (s) domain (Yamaoka et al. 1978; Ďurišová et al. 1995). In the last step the physiologically realistic structures of MRT_{po} and MRT_{im} are determined, using Eqs. (1), (2), the transfer functions $H_{po}(s)$, $H_{im}(s)$, the circulatory models developed, the method previously published (Ďurišová et al. 1995), and all assumptions made until now.

Results

The mean residence time of an intravenously administered drug

The physiologically realistic structure of MRT_{iv} determined is described by the following equation:

$$MRT_{iv} = F_{cp} + F_p + F_h + F_o + F_r. \quad (3)$$

As seen, the right-hand side of Eq. (3) contains five additive terms. The term F_{cp} describes the contribution to MRT_{iv} by the dynamic processes associated with the transport of the drug through the cardiopulmonary subsystem H_{cp}. The term F_p describes the contribution to MRT_{im} by the dynamic

process associated with the transport of the drug through the portal-venous subsystem H_p. The term F_h describes the contribution to MRT_{im} by the dynamic process associated with the transport of the drug through the hepatic-portal subsystem H_h. The term F_0 describes the contribution to MRT_{im} by the dynamic processes associated with the transport of the drug through the subsystem H_0. The subsystem H_0 mathematically represents drug fate and disposition in non-eliminating tissues. If the drug is subject to the enterohepatic circulation (EHC) (Shepard et al. 1989; Tvrdoňová et al. 2009), the term F_r describes the contribution to MRT_{im} by the dynamic processes associated with the transport of the drug through the subsystem H_r. The subsystem H_r mathematically represents the dynamic process associated with the EHC, and the terms F_p, F_h and F_0 are as follows:

$$F_p = \frac{Q_h - Cl_h}{Cl_h}\frac{Q_p}{Q_h} MT_p \tag{4}$$

$$F_h = \frac{Q_h - Cl_h}{Cl_h} MT_h \tag{5}$$

$$F_o = \frac{Q_o}{Cl_h} MT_o. \tag{6}$$

In Eqs. (4–6), Q_p is blood flow in the portal vein, Q_0 is blood flow in non-eliminating tissues, Cl_h is the hepatic clearance, MT_p is the mean transport time of the drug through the portal-venous subsystem, MT_h is the mean transport time of the drug through the hepatic-portal subsystem H_h, Q_h is blood flow in the hepetic subsystem, and MT_0 is the mean transport time of the drug through the subsystem H_0 where

$$MT_o = \frac{\sum_{i=1}^{q} Q_i . MT_i}{Q_o} \tag{7}$$

and finally MT_i is the mean transport time of the drug through non-eliminating tissues, the *i* subscript specifies a tissue (Valentinutzzi 1971; Waterhouse and Keilson 1972).

The mean residence times of a drug administered either orally (MRT_{po}) or intramuscularly (MRT_{im})

The circulatory models developed are shown in Fig. 1 and Fig. 2. The physiologically realistic structure of the mean residence MRT_{po} of an orally administered drug is described by the following equation

$$MRT_{po} = MT_s + MT_p + MT_h + MRT_{iv} \tag{8}$$

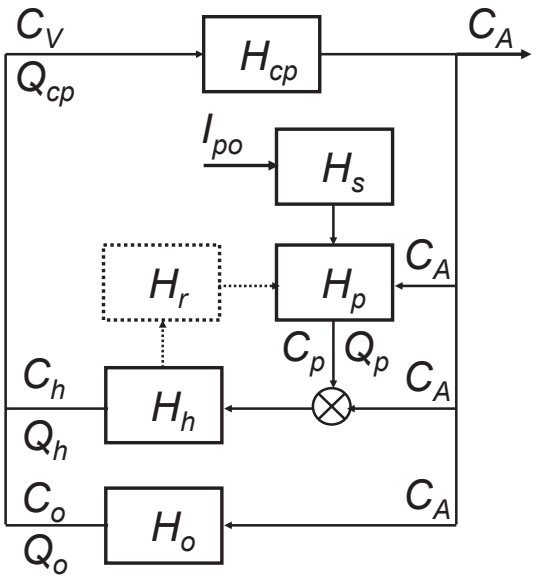

Figure 1. The circulatory model of the dynamic system H_{po} which mathematically represents dynamic process of drug fate and disposition after an oral drug administration. I_{po} is oral drug administration. C_A is the concentration-time profile of the drug in arterial blood. C_V is the concentration-time profile of the drug in venous blood. H_{pc} is the cardiopulmonary subsystem. H_p is the portal-venous subsystem. H_h is the hepatic subsystem. H_o is the subsystem representing non-eliminating tissues. H_r is the subsystem representing the enterohepatic cycling. C_p is the concentration-time profile of the drug in the subsystem H_p. C_h is the concentration-time profile of the drug in the subsystem H_h. C_o is the concentration-time profile of the drug in the subsystem H_o, O_{cp}, Q_p, Q_h, Q_o are the blood flows through the subsystems specified by a subscript. The symbol ⊗ denotes a summation operator.

In Eq. (8), MT_s is the mean transport time of the drug through the subsystem H_s. The subsystem H_s mathematically represents the following processes: disintegration of a tablet, the liberation of the drug from the tablet, drug dissolution, hepatic and intestinal first-pass effects (if present), and gastric emptying. MT_p is the mean transport time of the drug through the portal subsystem H_p. MT_h is the mean transport time of the drug through the hepatic-portal subsystem H_h. MRT_{iv} in Eq. (8) is the same as that in Eq. (3). The sum of the mean transport times $MT_s + MT_p + MT_h$ in Eq. (8) is mean transport time of the drug from the gastrointestinal tract to the blood circulation. If the drug is not subject to the EHC the term F_r in Eq. (3) is zero, and the term F_{cp} is as follows:

$$F_{po} = \frac{Q_{cp}}{Cl} MT_{cp} \tag{9}$$

If the drug is subject to the EHC, the term F_r in Eq. (3) is described by the following equation

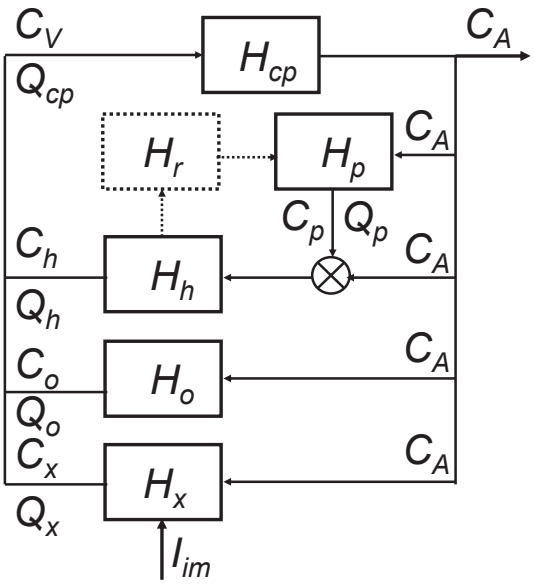

Figure 2. The circulatory model of the dynamic systems H_{im} which mathematically represents dynamic process of drug fate and disposition after an intramuscular administration. I_{im} is the intramuscular drug administration. For the meaning of other symbols, see Figure 1.

$$F_r = f_r \frac{Q_h - Cl_h}{Q_h - f_r Cl_h}(MT_p + MT_h + MT_r) \tag{10}$$

In Eq. (10) MT_{r} is the mean transport time of the drug through the subsystem H_{r} and the coefficient f_{r} where $0 \leq f_{\mathrm{r}} < 1$ is the fraction of the drug that is subject to the EHC.

The physiologically realistic structure of the mean residence MRT_{im} of an intramuscularly administered drug is described by the following equation

$$MRT_{im} = MT_x + MRT_{iv} \tag{11}$$

where MT_{x} is the mean transport time of the drug through the subsystem H_{x} i.e. the mean time of the transport drug from the injection site to the blood circulation. MRT_{iv} in Eq. (11) is the same as that in Eqs. (3) and (8).

Discussion

The current theoretical study is based on concepts borrowed from the theory of dynamic systems. Being a researcher in pharmacokinetics and using tools from the theory of dynamic systems is almost like begging for trouble. A quick look through handbooks on the theory of dynamic systems (see e.g. the books cited above) reveals an amassment of abstract terms and mathematical equations most of which are simply not accessible for a mathematically untrained reader, which a researcher in pharmacokinetics is likely to be. Therefore a prominent feature of the current theoretical study is its non-technical style which makes it easily accessible to a reader without any knowledge of the theory of dynamic systems. Moreover, the physiologically realistic structures determined are fairly simple, and contain only blood flows, *MRT*s, and clearances related to individual body parts. They do not require a sophisticated knowledge of the theory of dynamic systems understand them.

The theory of dynamic systems incorporates computational and experimental approaches, and provides a number of new visions, strategies, and practices for engineering in pharmacokinetics. This theory offers a framework for using general strategies to construct mathematical models of a wide variety of dynamic processes in pharmacokinetics such as dissolution, gastric emptying, absorption, etc.

Transfer functions are key tools to investigate dynamic systems in the theory of dynamic systems. A mathematical idea to describe drug fate and disposition with a transfer function is not recent. A transfer function was introduced to pharmacokinetics by Professor Giorgio Segré (Segré 1988).

Such a complicated dynamic process as drug fate and disposition cannot be exactly described by a mathematical model, and always there are inaccuracies in a model due to un-modeled characteristics of the modeled process. This is also the case for the circulatory models developed in the current theoretical study. In spite of this, using the circulatory models developed the physiologically realistic structures of MRT_{po} and MRT_{im} are successfully determined.

The circulatory model of the dynamic system H_{po} and the physiologically realistic structure of MRT_{po} reflect the fact that an orally administered drug has to pass through the gastrointestinal tract and liver before entering the blood circulation (Chiou 1983). This drug transport is mathematically represented by the subsystems H_{p}, H_{h} and H_{r} in the circulatory model of the system H_{po}. It follows then that, the circulatory model developed correctly approximates main processes in the body after an oral drug administration. In the circulatory model of the system H_{po} shown in Figure 2, the subsystem H_{r} is illustrated by dotted lines, because the EHC may be present or not present.

The *MRT*s, determined by conventional pharmacokinetic methods are single-number summaries for characteristics of responses of the body to drug inputs. In contrast the physiologically realistic structures of MRT_{po} and MRT_{im} may provide novel information not apparent from MRT_{po} and MRT_{im} determined by conventional pharmacokinetic methods. In this way the physiologically realistic structures of MRT_{po} and MRT_{im} may expand the understanding of MRT_{po} and MRT_{im}.

As can be seen in an overwhelming number of studies, *MRT*s, in spite of their approximate nature, have become valuable tools in pharmacokinetics (Cheng and Jusko 1989; Plusquellec and Houin 1990; Verotta et al. 2001; García-Meseguer et al. 2003). Taking into account this fact, the goal of the current theoretical study was to introduce the physiologically realistic structures of *MRT*s to pharmacokinetics.

The current theoretical tries to arouse interest of researchers and practitioners in pharmacokinetics and in physiology in the theory of dynamic systems. Differences between traditional pharmacokinetic approaches and approaches based on the theory of dynamical systems to *MRT*s are left unexplained. Instead of a comparison between approaches, the current theoretical study gives rise to a reasonable expectation that the use of the structures determined for the enhancing understanding of *MRT*s is not a utopian goal. The physiologically realistic structures determined have not been experimentally validated up to now. Their validity can be verified by further investigations, mainly experimental investigations. For this reason a full pharmacokinetic exploitation of the structures of MRT_{po} and MRT_{im} lies far in the future.

In this study an attempt is made to contribute to the theoretical base of pharmacokinetics, without an intention to criticize traditional approaches to MRT_{po} and MRT_{im}.

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