



Research Article

A Further Example Showing Efficiency of a Modeling Method Based on the Theory of Dynamic Systems in Pharmacokinetics

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Keywords: Dynamic system; Mathematical model; Transfer function

Abbreviations: ADME: Absorption Distribution Metabolism Excretion; CTDB: Clinical Trials Data Base



ABSTRACT

Aims: To present a further example showing an efficiency of a modeling method based on the theory of dynamic systems in pharmacokinetics.

Study design: The goals of the current study were twofold: to present (1) a further example showing efficiency of a modeling method based on the theory of dynamic systems in pharmacokinetics, and to perform (2) a next step in tutoring the use of computational and modeling tools from the theory of dynamic systems in pharmacokinetics.

The data available in the study by Plusquellec et al. published in the October Issue of the Journal Medical Engineering & Physics were used to exemplify the method considered here. For modeling purpose an advanced mathematical modeling method was employed. Modeling was performed using the computer program named CTDB described in the study by Dedik et al. published in September 2007 issue of the Journal Diabetes Research and Clinical Practice.

Main outcome: Modeling results revealed that computational and modeling tools from the theory of dynamic systems can be successfully used in the development of a mathematical model of such a complicated process as is a multiple sites discontinuous gastrointestinal absorption.

INTRODUCTION

Ranitidine is a histamine H₂-receptor antagonist with a potent and long-acting antisecretory effect in humans that significantly improves the quality of gastric ulcer healing and histological scores of gastric mucosa in patients with gastric ulcers. In addition, ranitidine was successfully utilized in the treatment of active duodenal ulcers and gastric hypersecretory, where the inhibitory effect of ranitidine on the gastric secretion was much longer than that of cimetidine. Ranitidine is a widely used drug and is known to be well tolerated by patients. Ranitidine is commonly used in treatment of peptic ulcer disease, gastroesophageal reflux disease, and Zollinger-Ellison syndrome it is possibly more effective than cimetidine [1-10].

The goals of the current study were twofold: 1) to present a further example showing efficiency of a modeling method based on the theory of dynamic systems in pharmacokinetics; 2) to exemplify the modeling method considered here, using the data available in the study by Plusquellec et al. published in October 1999 Issue of the Journal Medical Engineering & Physics.

METHODS

The data available in the study cited above employed. For modeling purposes the computer program named CTGB described in the study by Dedík et al. published in September 2007 issue of the Journal Diabetes Research and Clinical Practice was employed.

Throughout the current study, the lower case letter “*S*” was used for the complex Laplace variable [10-24]. The development of a mathematical model of the pharmacokinetic behavior of ranitidine [1-9] was performed in the following successive steps:

(1) The definition of an ADME-related dynamic pharmacokinetic system [25] denoted by *H*, using: the Laplace transform of the mathematically described serum concentration-time profile of ranitidine, denoted by *C*(*s*), and the Laplace transform of the mathematically described oral administration of ranitidine [7], denoted by *I*(*s*). In the definition of the ADME-related dynamic pharmacokinetic the profile *C*(*s*) and the profile *I*(*s*) was used as the output and input, respectively, of the ADME-related dynamic pharmacokinetic system *H* [10-24].

(2) The introduction of the following simplifying assumptions: a) initial conditions of the ADME-related dynamic pharmacokinetic system were zero; b) all processes mathematically described by the ADME-related dynamic pharmacokinetic system were linear and time invariant [10-24]; c) concentrations of ranitidine were the same throughout all subsystems of the ADME-related dynamic pharmacokinetic system, (where each subsystem was an integral part of the ADME-related dynamic pharmacokinetic system).

(3) The static and dynamic properties of the pharmacokinetic behavior of orally administered ranitidine [25-27] were described with the ADME-related dynamic pharmacokinetic system;

(4) The transfer function, denoted by *H*(*s*), of the ADME-related dynamic pharmacokinetic system was derived, using the profiles *C*(*s*) and *I*(*s*), see Eq. (1).

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

(5) The ADME-related dynamic pharmacokinetic system was described with the transfer function *H*(*s*) in the complex domain.

In the following text, the ADME-related dynamic pharmacokinetic system was simply called the dynamic system

(6) The mathematical model of the dynamic system was developed using the computer program named CTDB [15] and the transfer function model *H_M*(*s*) described by the following equation:

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

On the right-hand-side of Eq. (2) is the Padé approximant [28,29] of the mathematical model of the transfer function *H_M*(*s*), *G* is an estimator of a model parameter called a gain of a dynamic system, *a*₁, ..., *a*_{*n*}, *b*₁, ..., *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, *n* is the highest degree of the nominator polynomial, and *n* < *m* [see Eq. (2)] [9-24].

(7) The transfer function *H*(*s*) was converted into equivalent frequency response function, denoted by *F*(*iω*) [29].

Table 1: Parameters of the fourth-order model of the dynamic system describing the dynamic pharmacokinetic behavior of orally administered ranitidine [1].

Model parameters	Estimates of model parameters	(95% CI)
G (h. ⁻¹)	0.0097	0.006 to 0.012
a ₀ (-)	0.923	0.825 to 1.024
a ₁ (min)	69.15	45.12 to 72.38
b ₁ (min)	421.88	391.73 to 462.02
b ₂ (min ²)	6043.61	7028.59 to 6059.33
b ₃ (min ³)	3478275.74	3478271.05 to 3678280.33
b ₄ (min ⁴)	5825685.25	29456822.06 to 6234685.25

Table 2: Model-based estimates of pharmacokinetic variables of orally administered ranitidine [1].

Primary pharmacokinetic variables	Estimates of primary pharmacokinetic variables
The half-time of Ranitidine t _{1/2} (hod)	1.5±0.4*
Clearance of ranitidine (ml/min)	103.1±15.3
Renal clearance of ranitidine (ml/min)	74.1±5.1
Body clearance of ranitidine (ml/min)	218±8.1
Elimination half-life of ranitidine (hr)	51.6±5.4
Distribution volume of ranitidine (l)	681±9.5
AUC _{0→∞} (ng.h/ml)	26.95

*standard deviation

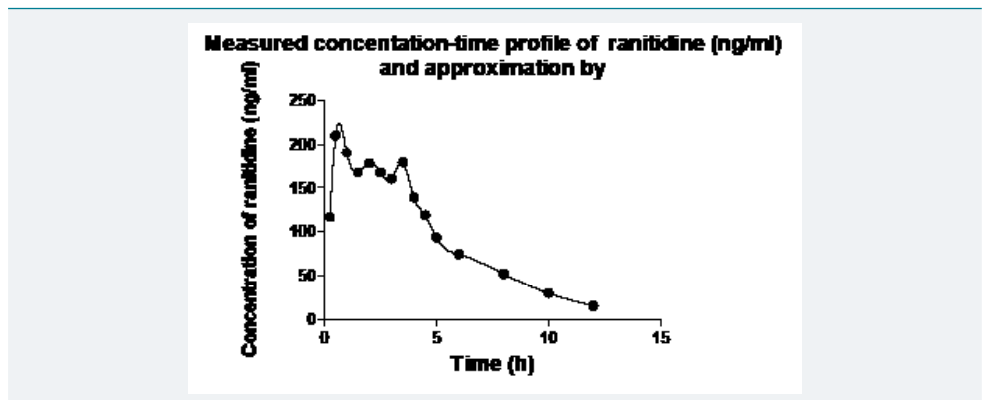


Figure 1: Patient 24, varying maximum activity in visual comparison of I-131 scintigram (1a) with the Tc-99m-O₄ scintigram (1b). Grid image in Figure 1a highlighted by the use of a high-energy collimator.

(8) The non-iterative method described in the study published previously [29] was used to develop a mathematical model of the frequency response function $F_M(i\omega_j)$ and to determine point estimates of parameters of the model of the frequency response function $F_M(i\omega_j)$ 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:

$$F_M(i\omega_j) = G \frac{a_0 + a_1 i\omega_j + \dots + a_n (i\omega_j)^n}{1 + b_1 i\omega_j + \dots + b_m (i\omega_j)^m} \tag{3}$$

Analogously as in Eq. (2), n is the highest degree of the numerator polynomial of the model of the frequency response function $F_M(i\omega_j)$, m is the highest degree of the denominator polynomial of the mathematical model of the frequency response function $F_M(i\omega_j)$, $n \leq m$, i is the imaginary unit, and ω is the angular frequency in Eq. (3).

The Akaike information criterion, modified for the use in the complex domain [9,30] was employed to select the best mathematical model of the frequency response function $F_M(i\omega_j)$ and to determine point estimates of the parameters of the best mathematical model of the frequency response function $F_M(i_j)$.

Finally, the Monte-Carlo and the Gauss-Newton method [31,32] were used to refine the mathematical model of the frequency response function $F_M(i\omega_p)$ and to determine 95 % confidence intervals of the parameters of the best mathematical model of the frequency response function $F_M(i\omega_p)$ in the time domain.

After the development of the best mathematical model $F_M(i\omega_p)$ of the dynamic system investigated, the following primary pharmacokinetic variables of ranitidine were determined: the elimination half-time of ranitidine, denoted by $t_{1/2}$, the area under the serum concentration-time profile of ranitidine from time zero to infinity, denoted by $AUC_{0-\infty}$ and total body clearance of ranitidine, denoted by Cl .

The mathematical model of the transfer function $H_M(s)$ and the mathematical model of the frequency response function $F_M(i\omega_p)$ are implemented in the computer program CTDB [15]. 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>

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