

Evaluation of Arterial-Venous Blood Alcohol Concentration Gradients of Ethanol Administered by an Infusion to Dogs

Maria Durisova*

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

Abstract

Numerous workers investigated ethanol pharmacokinetic. Therefore, the goal of the present study was not an investigation of ethanol pharmacokinetics; instead, the goal of the present study was to prepare further illustrative examples of a successful use of computational and modeling tools from system engineering in pharmacokinetic investigations.

The previous study by Wilkinson and Rheingold published in October 1977 issue of the Journal of Pharmacokinetics, described an investigation of arterial-venous blood concentration gradients of ethanol administration by a constant rate intravenous infusion through indwelling venous catheters to dogs.

The present study is a free continuation of the study by Wilkinson and Rheingold; therefore, the data available in the study by Wilkinson and Rheingold were used.

An advanced modeling method, implemented in the computer program named CTDB, and described in the study by Dedik *et al*^[1] was used for modeling purposes.

Keywords: Dynamic system; Mathematical model

Introduction

Ethanol, has been used medicinally and recreationally and its pharmacokinetic properties have been studied widely for medical, legal and forensic purposes.

Numerous studies published previously described investigations of the pharmacokinetic behavior of ethanol using traditional pharmacokinetic modeling method^[2-8]. Therefore, the goal of the present study was not to investigate ethanol pharmacokinetics; instead, the goal of the present study was to prepare further illustrative examples of a successful use of modeling and computational tools from system engineering in pharmacokinetic investigations. The previous examples can be find in the full-text articles that are available free of charge at the following web site of the author: <http://www.uef.sav.sk/durisova.htm>

In the preparation of illustrative examples, the data available in the study by Wilkinson Rheingold and an advanced modeling method implemented in the software named CTDB were used^[1].

An example of a successful use of the computer CTDB can be find in the study by Dedik *et al.* published in September 2007 Issue of the Journal Diabetes Research and Clinical Practice, which is available here:

http://www.uef.sav.sk/advanced_files/OGTT-2007.pdf

The mathematical models developed in the present study, successfully described observed ethanol concentration-time profiles of ethanol of the dogs investigated in the study by Wilkinson and Rheingold^[8] and in the present study.

Methods

The data of dogs taken from the study by Wilkinson and Rheingold were used.

The advanced mathematical modeling method described in the study by Dedik *et al*^[1], published in September 2007 Issue of the Journal Diabetes Research and Clinical Practice and implemented in the computer program named CTDB was employed for modeling purposes^[1]. The demo

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***Corresponding author:** Maria Durisova, Slovak Academy of Sciences, Institute of Experimental Pharmacology and Toxicology, Bratislava, Slovak Republic, Tel: 002412;
E-mail: maria.durisova@savba.sk

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version of the computer program CTDB can be finding on the following author's web site: <http://www.uef.sav.sk/advanced.htm>

The development of mathematical models of the concentration-time profiles of ethanol after ethanol infusion to the dogs investigated in the study^[2] and in the present study was performed as described later on:

On the first step of the model development process, an ADME related dynamic system was defined in Laplace domain for the dogs, using the transfer function, denoted by $H(s)$ and described by Eq. (1):

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

In Eq.(1): S is the Laplace variable, $I(s)$ is the Laplace domain counterpart of the mathematically transformed intravenous administration of ethanol to the dogs^[2] and $C(s)$ is the Laplace domain counterpart of the mathematically transformed blood ethanol concentration time profile measured following intravenous administration of ethanol to the dogs investigated in the study^[2] and in the present study.

On the second step of the model development process, a mathematical model of the dynamic system defined was developed, using the advanced modeling method implemented in the computer program named CTDB^[1].

The general form of the model transfer function $H_M(S)$ used also in the present study, is described by the following equation:

$$H_M(s) = G \frac{a_0 + a_1s + \dots + a_n s^n}{1 + b_1s + \dots + b_m s^m} \quad (2)$$

On the right-hand-side of Eq. (2) is the Padé approximant to the model transfer function $H_M(S)$ ^[9,10],

G is an estimator of the model parameter conventionally called a gain of a dynamic system, $a_1, \dots, a_n, b_1, \dots, b_m$ 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 for example the studies^[11-27] and references therein.

On the third step of the model development process, the model transfer function was converted into the equivalent model frequency response function (denoted by $F_M(I\omega_j)$) in the frequency domain; see for example, the studies cited above.

After that, the previously published non-iterative method^[28] was employed to determine the model frequency response function $F_M(I\omega_j)$ of the dogs, and to determine point estimates of the parameters of the model frequency response function $F_M(I\omega_j)$ in the frequency domain. The general form of a model the frequency function $F_M(I\omega_j)$ is described by Eq. (3). It was also used in the current study.

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

Besides the radial frequency ω and the imaginary unit i , the meaning of the symbols used in Eq. (3) is the same as the meaning of the symbols used in Eq. (2)

On the fourth step of the model development process, the best model of the frequency response function $F_M(I\omega_j)$ was selected using the Akaike information criterion, modified for the use in

the complex domain^[29,30].

On the fifth step of the model development process, a) the output $C(s)$ of the model developed corresponding to the ethanol input $I(s)$ was determined, using a numerical simulation method in the time domain;

After that the model output $C(s)$ was refined, using the Gauss-Newton and Monte-Carlo method^[31,32] in the time domain.

After that, the outcomes of the models developed and the concentration-time profiles of ethanol were mutually statistically compared, and in this way, a validation on the models was performed^[33-38].

Results

As seen in Figures 1 - 4, the mathematical models developed successfully described

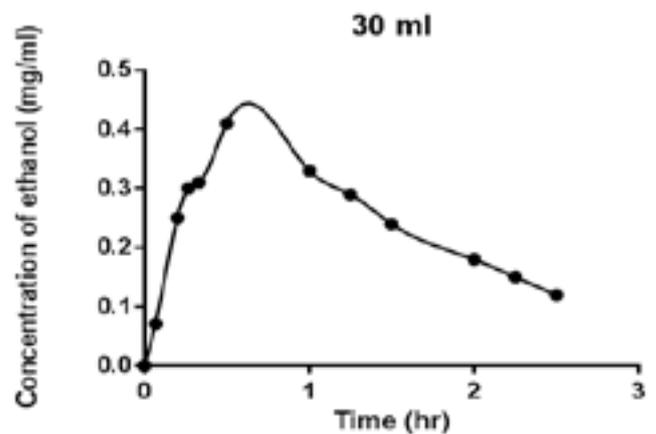


Figure 1: Blood ethanol concentration-time profile measured after intravenous infusion of ethanol to dogs^[1] and the model developed.

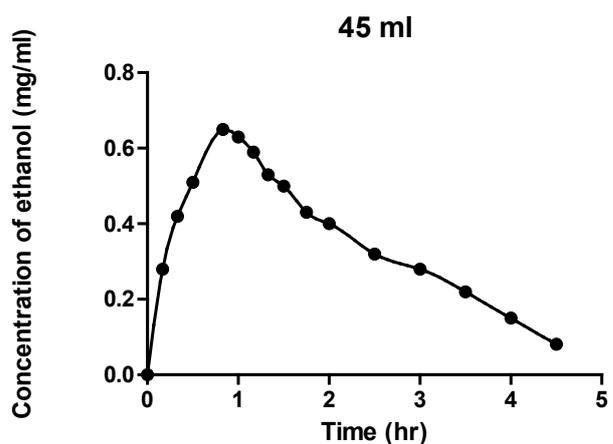


Figure 2: Blood ethanol concentration-time profile measured after intravenous infusion of ethanol to dogs^[1] and the model developed.

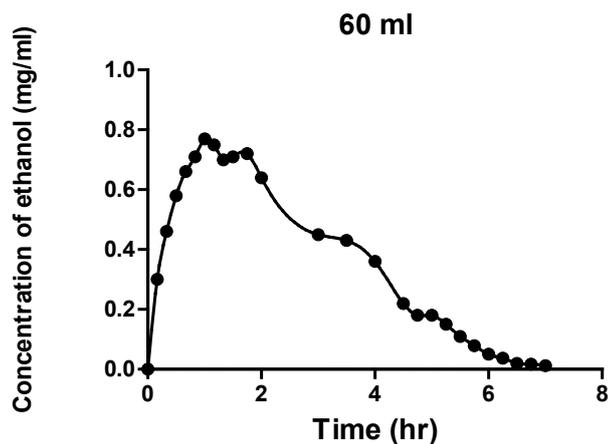


Figure 3: Blood ethanol concentration-time profile measured after intravenous infusion of ethanol to dogs^[1] and the model developed.

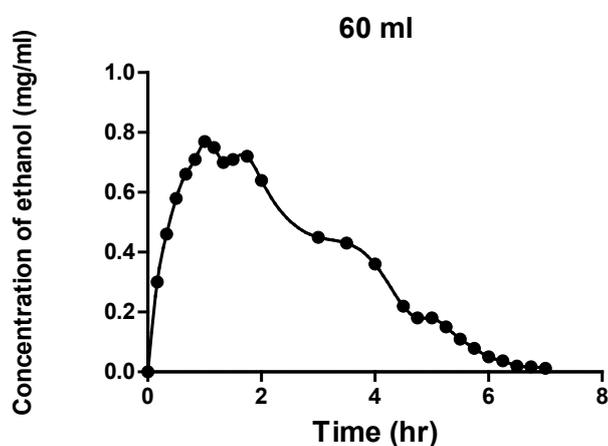


Figure 4: Blood ethanol concentration-time profile measured after intravenous infusion of ethanol to dogs^[1] and the model developed.

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