SciDoc Publishers
Infer, Interpret & Inspire Science

OPEN ACCESS

International Journal of Clinical Pharmacology & Toxicology (IJCPT)
ISSN 2167-910X

Decomposition of Concentration-Time Profiles after Oral Administration of Different Ethanol Doses in Humans

Review Article

Chrenova J[1*], Dedik L[1], Rausova Z[1], Edita Hlavacova[1], Paul K. Wilkinson[2]

[1] Faculty of Mechanical Engineering, Slovak University of Technology, Bratislava, Slovakia
[2] President, WILKINSON CHEM-PHARM SOLUTIONS, LLC, Cincinnati, OH

Abstract

A new physiologically-motivated structural model capable of evaluating ethanol behavior within the whole-body blood metabolism was developed. This model was estimated on the basis of a reanalysis of the mean blood ethanol concentration-time profile data after the oral administration of 11.2, 22.4, 33.6 and 45 g ethanol doses to eight fasting adult male volunteers published in the study of Wilkinson et al. from 1977. From the system theory point of view, our structural model is a linear flow well-stirred model characterized by parameters: time delay, time constant, clearance and blood flow considered for construction of the gastrointestinal and circulatory system. This model explains the linear increasing of mean residence time and gain of the system, and nonlinear increasing of area under curve and blood flow through the cardiopulmonary subsystem depending on the administered ethanol dose. The number of absorbed ethanol fractions dependent on the dose was within 3 to 5.

Keywords: Blood ethanol concentrations; Ethanol absorption; Gastric emptying; Mechanistic-circulatory model; Oral ethanol dosing.

***Corresponding Author**:
Jana Chrenova,
Institute of Automation, Measurement and Applied Informatics,
Faculty of Mechanical Engineering, Slovak University of Technology,
Namestie slobody 17, 812 31 Bratislava 1, Slovak Republic;
Tel: +421 2 524 95 315; Fax: +421 2 524 95 315.
E-mail: jana.chrenova@stuba.sk

Received: February 18, 2013

Accepted: February 27, 2013
Published: February 27, 2013

Citation: Chrenova J, Dedik L, Rausova Z, Edita Hlavacova, Paul K. Wilkinson (2013) Decomposition of Concentration-Time Profiles after Oral Administration of Different Ethanol Doses in Humans. Int J Clin Pharmacol Toxicol. 2(2), 47-53. **doi:** http://dx.doi.org/10.19070/2167-910X-130001

Introduction

The main initiative to undertake this reanalysis work was based on the publication in the bulletin NIAAA *Alcohol Alert* of National Institute on Alcohol Abuse and Alcoholism [1], which involved the results of the simultaneous fitting of the average blood alcohol concentration after the oral administration of different amounts of alcohol to eight fasting adult male volunteers according to study of Wilkinson and his research group [2]. Wilkinson's model is applicable to average blood alcohol concentration data of subjects listed in full numeric form in this work. Wilkinson's model represents the application of a one compartment open model with Michaelis-Menten elimination kinetics and one absorption site and an absorption fraction dependent on the administered ethanol dose. It was the basis for pharmacokinetic modeling of ethanol behavior in the human beings presented in many subsequent studies [3-6].

The aim of our work includes the physiological-based explanation of the AUC (area under curve) and MRT (mean residence time) increase observed with increasing ethanol dose by considering mathematical considerations different that the general assumption of Michaelis-Menten elimination ethanol kinetics.

Our work is based on the hypothesis for a mathematical model construction included the first pass effect of ethanol in the gastrointestinal tract and liver, especially the assumption of ethanol absorption occurring in the stomach and not only in the small intestine (Fig.1), and the mechanistic-circulatory model of the circulatory system presented below (as Mathematical model structure) in Fig.2. This hypothesis is closely related to Wilkinson's study [2] with the main aim to explain the background and quantification of multiple waves of average blood ethanol concentration profiles of presented study due to the gastrointestinal tract, or to possible errors of concentration profile's measurements.

The main tool of the presented mathematical modeling and analysis is based on linear dynamic system theory and computer simulation implemented in the method CCSS (Computer controlled sequential simulation) [7] that were presented in previous works [8,9].

Materials and Methods

Subjects

Eight healthy white male volunteers (age: 21-27 years, weight: 66-89 kg) participated in the Wilkinson`s study [2]. According to the specific dosage schedule at 1-week intervals, each volunteer was orally administered 15, 30, 45 and 60 ml of 95% ethanol in 150 ml of orange juice. The subjects fasted from 10h pre-dose until 3h post-dose of alcohol. Except for prescribed alcohol, they abstained from drinking any alcohol beverages from 3 days prior to

the start of each study phase until the end of the phase. All trials were approved by the in-house Institutional Review Board (IRB) at the University of Michigan Hospital. All trails were conducted in a facility at the University of Michigan hospital complex. All subjects completed Informed Consent Forms.

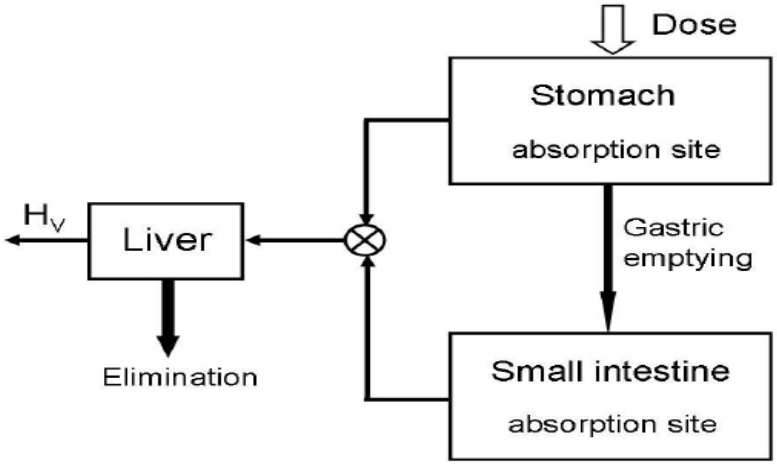
Prior to dosing and the sampling times following the 15, 30, 45 and 60 ml doses of 95% ethanol, 18, 25, 23 and 27 capillary blood samples, respectively, were taken. The samples were collected from a fingertip in a 50 µl calibrated micro-sampling capillary tube, mixed and kept in the frozen state until analyzed according to a sensitive and specific head-space gas chromatographic method The analysis of the samples was carried out on a Varian 2100 gas chromatograph equipped with flame ionization detectors [2].

The administered doses D of 15, 30, 45 and 60 ml of 95% alcohol were considered in the following analysis as 11.2, 22.4, 33.6 and 45.0g of absolute alcohol, respectively.

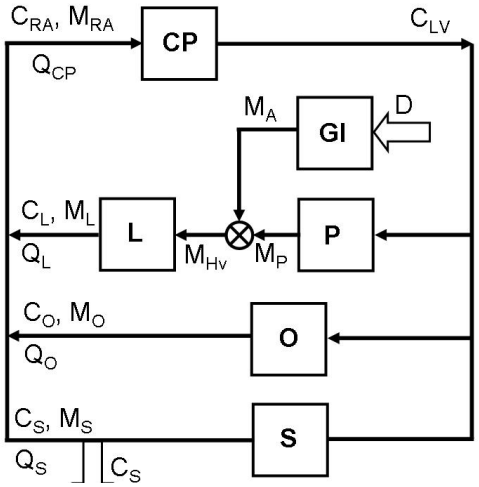
Mathematical model structure

The structure of the mathematical model of ethanol behavior in the body (Fig. 2) was selected by the tools of mathematical modeling and analysis based on the linear dynamic system theory implemented in CTDB software (Clinical Trials Database). The structural model includes model of the gastrointestinal subsystem GI, and a mechanistic-circulatory model of the circulatory system containing the liver subsystem L, the cardiopulmonary subsystem

Figure. General scheme of the first pass metabolism of ethanol. HV - hepatic vein



Fgure 2. Structural model of gastrointestinal subsystem and circulatory system of ethanol.
D - ethanol dose; GI - gastrointestinal subsystem; L - liver subsystem; P - portal subsystem; CP - cardiopulmonary subsystem; S - sampling subsystem; O - other subsystems; Q - blood flow; C - ethanol concentration;M - ethanol amount; RA - right atrium; LV - left ventricle; Hv - hepatic vein.



CP, the portal subsystem P, the sampling subsystem S (e.g. perifierial circulation), and other subsystems O.

When it is assumed that the all significant subsystems shown in Fig.2 are within the measured concentrations formalized as linear dynamic systems, then i-subsystems can be described by the transfer function , which is a general mathematical model of a subsystem presented by a well-stirred model with time delay as

$$H_i(s) = \frac{g_i}{T_i s + 1} e^{-\tau_i s}$$

where s is the Laplace operator, T is the time constant of the subsystem and is the time delay of the subsystem.

For g_i constant it is generally valid that

$$gi = \lim_{s \to \infty} H_i(s)$$

If Cl_i is the subsystem clearance and Qi is blood flow i.e., plasma flow by subsystem, respectively then for gi it is valid that

$$gi = 1 - Cl_i / Qi$$

If $Cl=0$ then $gi=1$; otherwise $gi < 1$

Transfer function H_{GI} of the GI tract comprising absorption and gastric emptying GE, is defined as

$$H_{GI}(s)=M_A(s)/D(s)$$

where D(t)=Dose.δ(t). δ(t) is the Dirac function and M_A is absorbed amount per unit of time in the GI subsystem during the first pass metabolism of the ethanol. Consequently, the presented subsystem can be described by the model structure according to

$$H_{GI}(s)=\frac{F_1}{T_1 s+1}e^{-\tau_1 s}+\frac{1}{T_2 s+1}\sum_{j=2}^{5}F_j e^{-\tau_j s}$$

where F1 and T1 are the ethanol fraction and time delay of absorption site AS1 (stomach), Fj and τ_j are the ethanol fraction and time delay of absorption site AS2 (small intestine).

For ethanol concentration in the right atrium C_{RA} is valid that

$$C_{RA}(t)=\frac{C_L(t)Q_L+C_O(t)Q_O+C_S(t)Q_S}{Q_{CP}}=\frac{M_L(t)+M_O(t)+M_S(t)}{Q_{CP}}$$

where QCP is the blood flow through the cardiopulmonary system expressed by the form

$$Q_{CP}=Q_L+Q_O+Q_S$$

and Q_L, Q_O and Q_S are blood flow via liver, other and sampling subsystems, respectively.

Pursuant to the symbolism in Fig. 2, M is the amount of ethanol per unit of time that is possible for the models of other subsystems to consider (as inputs) following transfer functions, respecting the mass balance.

The definition of the cardiopulmonary subsystem CP and the model in the transfer function form is expressed as follows

$$H_{CP}(s)=\frac{C_{LV}(s)}{M_{RA}(s)}=\frac{1}{Q_{CP}}$$

where C_{LV} is the ethanol concentration in the left ventricle, MRA is the ethanol amount in the right atrium and QCP is the blood flow through the cardiopulmonary system.

The definition of the portal subsystem P and the model in the transfer function form is expressed as follows

$$H_P(s)=\frac{M_P(s)}{M_{RA}(s)}=\frac{g_p Q_p}{T_p s+1}$$

where M_P, g_P, Q_P and T_P are the ethanol amount, gain, blood flow and time constant related to the portal subsystem.

The definition the liver subsystem L and the model in the transfer function form is expressed as follows

$$H_L(s)=\frac{M_L(s)}{M_{Hv}(s)}=\frac{g_L}{T_L s+1}$$

where M_{Hv} is the ethanol amount in the hepatic vein, M_L, g_L and T_P are the ethanol amount, gain and time constant related to the liver subsystem.

The definition of the other (i.e. passive) subsystem O and the model in the transfer function form are expressed as follows

$$H_O(s)=\frac{M_O}{C_{LV}}\sum_{i=1}^{m}\frac{g_i Q_i}{T_i s+1}.e^{-s\hat{o}_i}$$

where is number of passive model subsystems, MO is the ethanol amount in the other subsystem, CLV is the ethanol concentration in the left ventricle, g_i, Q_i, T_i and τ_j are the gain, blood flow, time constant and time delay related to the subsystem.

The model for the peripheral sampling subsystem S was thought to be an ideal subsystem for which it is valid

$$H_S(s)=1$$

Employing the parameters of the developed structural mathematical model (Fig. 2), the vector λ of estimated parameters was determined as follows

$$ë=(F_1,F_2,F_3,F_4,F_5,\hat{o}_1,\hat{o}_2,\hat{o}_3,\hat{o}_4,\hat{o}_5,\hat{o}_{O1},\hat{o}_{O2},T_1,T_2,T_L,T_P,T_{O1},T_{O2},G_P,G_{O1},G_{O2})$$

where F_1, τ1 and T_1 are the ethanol fraction, time delay and time constant of absorption site AS1 (stomach); F_2 - F_5, τ_2 -τ_5 and T2 are the ethanol fractions, time delays and time constant, respectively, related to the absorption site AS2 (small intestine); τ_{O1} - τ_{O2}, T_{O1} - T_{O2}, G_{O1} - G_{O2} are the time delays, time constants and gains, respectively, related to the other subsystem; T_L and T_P are time constants of the liver and portal subsystems, respectively; G_P is the gain of the portal subsystem.

To estimate the model parameters, the Monte Carlo method as implemented in CCSS method (Computer controlled sequential simulation) [7] were used.

The number *m* of the other, passive subsystems of circulatory system and the number of fractions *n* for the optimal model were particularly detected for the individual ethanol dose on the base of minimal value of Akaike's information criterion [10].

Based on the estimation of parameter vector λ, the simulation of the model was performed and the gain of the system G was defined as

$$G=\frac{\int_0^{\infty}C(t)\,dt}{D}$$

and may be calculated as $$G=\frac{1}{Q_{CP}-\sum_{i=1}^{3}G_i}$$

where Q_{CP} is the blood flow through the cardiopulmonary subsystem and Gi includes G_P, G_{O1}, G_{O2} parameters.

For the mean residence time of the ethanol of the whole body MRT_w after oral administration is valid that

$$MRT_W = MRT_{GI} + MRT_{circ}$$

where MRT_{GI} is mean residence time of gastrointestinal subsystem and MRTcirc is mean residence time of circulatory system.

The MRTGI parameter is expressed by the form

$$MRT_{GI} = (T_1 + \tau_1)F_1 + T_2\sum_{i=2}^{5}F_i + \sum_{i=2}^{5}F_i\tau_i$$

where T1 and T2 are the time constants of absorption sites AS1 and AS2, respectively, τ is time delay of the subsystem and F represents the absorbed ethanol dose fractions.

Mean residence time of ethanol in the circulation system MRTcirc is calculated according to relation

$$MRT_{circ} = MRT_w - MRT_{GI}$$

The parameter MRT of the whole system is calculated numerically as

$$MRT = \frac{\int_0^{t_r} t.C(t)dt}{\int_0^{t_r} C(t)dt}$$

where r is the number of measured points in the terminal phase of concentration-time profile (e.g. the elimination phase).

Considering the models of Hi subsystems, where i = P (P is portal subsystem, and O are other subsystem), the contents of the product of parameters gi, Qi can not be individually identified, therefore only parameters $Gi=giQi$ is estimated.

In the case of analogous serially ordered L and P subsystems is not possible to obtain an individual estimate of g_L and G_p parameters and then the parameter $g_L = 1$ must be considered.

The rate constant of absorption ka1 of absorption site AS1 is expressed as follows

$$k_{a1} = \frac{1}{T_1}$$

where T1 is the time constant of absorption site AS1.

The rate constant of absorption ka2 of absorption site AS2 is expressed as follows

$$k_{a2} = \frac{1}{T_2}$$

where T2 is the time constant of absorption site AS2.

The rate constant of elimination ke is expressed as follows

$$k_e = \frac{1 - \frac{G_P}{Q_{CP}}}{T_2 + T_L + T_P}$$

where G_P is the gain of the portal subsystem, Q_{CP} is the blood flow through the cardiopulmonary subsystem, T_2 is the time constant of absorption site AS2, T_L is the time constant of liver subsystem and T_P is the time constant of portal subsystem.

Results

Summaries of the dependence of the absorbed ethanol dose fraction, the time delay and the time constant parameters on the four oral administered ethanol doses are shown in Fig.3a, b, c. On the basis of Akaike's information criterion [10], the optimal fraction numbers $n = 3, 4, 4, 5$ for ethanol doses 11.2, 22.4, 33.6 and 45g, respectively, were detected (Fig.3a).

The decompositions of the average ethanol concentration-time profiles after the oral administration of 11.2g and 45g ethanol doses are described in detail in Fig. 4a, b. Presented decompositions describe multiple waves of the ethanol concentration-time profile representing F_1 to F_n fractions, and closely associated with Fig.3a, b, c. The model of the whole concentration-time ethanol profile is expressed by the form

$$C(t) = \sum_{i=1}^{n} C_i(t)$$

where for 11.2g ethanol dose is valid $n=3$ and for 45g ethanol dose is valid $n=5$; C1 represents the model expressed F_1 fraction related to the absorption site AS1, C_2 to C_n represent the model expressed F_2 to F_n fractions related to the absorption site AS2.

The representation of the relationship between AUC, G parameters and four different ethanol doses after oral administration to eight fasting male subjects is depicted in Fig.5a, b. The dependence of AUC and G parameter on ethanol doses was analyzed by quadratic parabola (Fig.5a) and linear line (Fig.5b), respectively.

Figure 6 includes the regression analysis results of mean residence time of the whole body MRTw (circles and solid line), mean residence time related to gastrointestinal subsystem MRTGI (squares and dashed line) and circulatory system MRTcirc (triangles and dotted line) depending on the dose. The dependence of parameters MRT on ethanol doses is expressed by single line.

The overview of rate constants of absorption k_{a1} and k_{a2} and rate constants of elimination ke and ke according to Wilkinson`s study [2] and k_e** estimated from the measured r-points in the terminal phase of ethanol concentration-time profile by exponential function depending on four oral administered doses is listed in Table 1.

Discussion

The measured blood ethanol concentration-time profiles from the data of the Wilkinson et al. [2] study are approximated by a physiologically-motivated structural model of a gastrointestinal subsystem and circulatory system (Fig.2) aimed to provide the estimation of physiologically interpretable parameters and

Figure 3. Comparison of the absorbed dose fraction, the time delay and the time constant parameter dependence on four oral ethanol doses administrated to eight male adult subjects. 3a) F1 - dose fraction related to AS1 (stomach); F2 - Fn, where n is the fraction number - dose fractions related to AS2 (small intestine); 3b) τ1 - time delay related to AS1; τ2, τ3, τ4, τ5 - time delays related to AS2; 3c) T1 - time constant related to AS1; T2 - time constant related to AS2; AS1, AS2 - absorption sites.

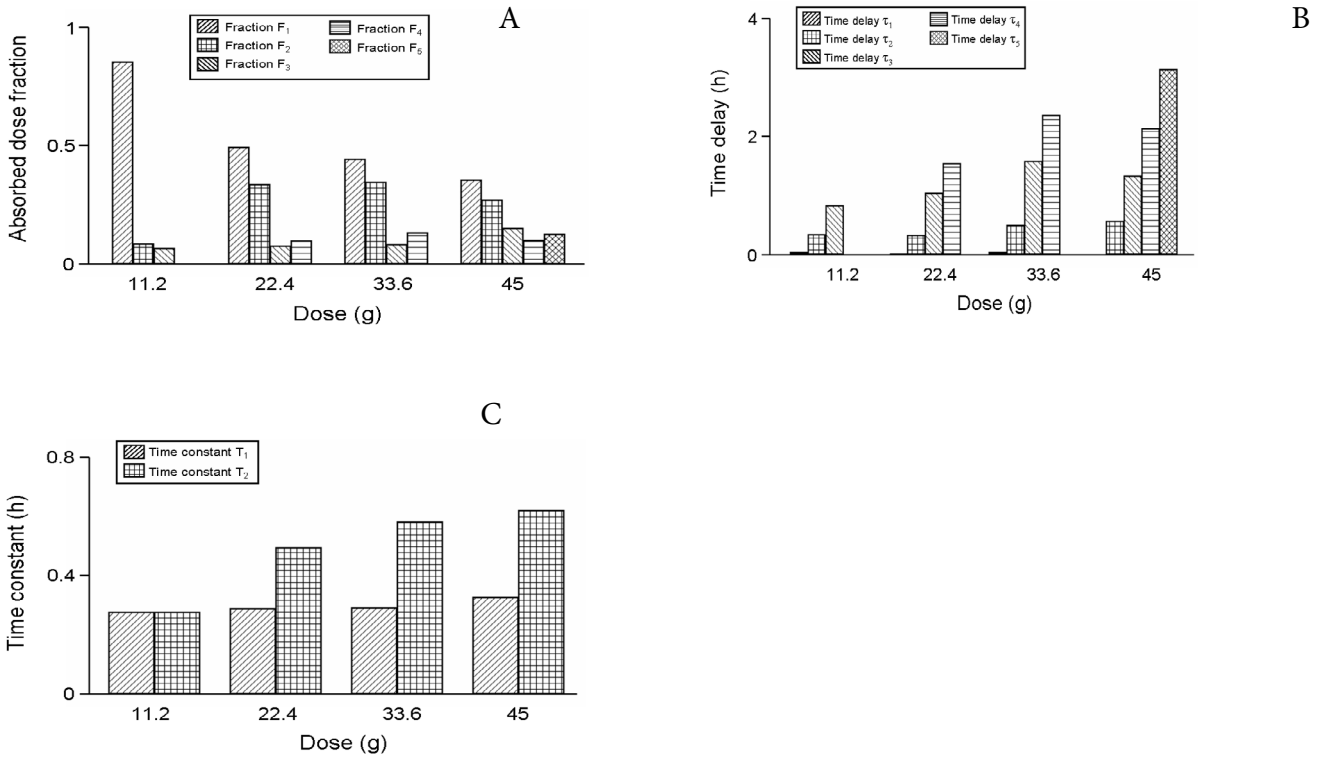


Figure 4. Decomposition of mean blood ethanol concentration-time profile with multiple waves of fractions following the oral administration of the doses of 11.2g (a) and 45g (b) of absolute ethanol to eight male adult subjects. Circles - mean measured blood ethanol concentration; solid line C - the model predicted mean concentration-time profile; 4a) solid lines C_1 to C_3 - the model predicted blood ethanol concentration-time profile expressed for fractions F_1 to F_3; 4b) solid lines $C_1$to C_5 - the model predicted blood ethanol concentration-time profile expressed for fractions F_1 to F_5.

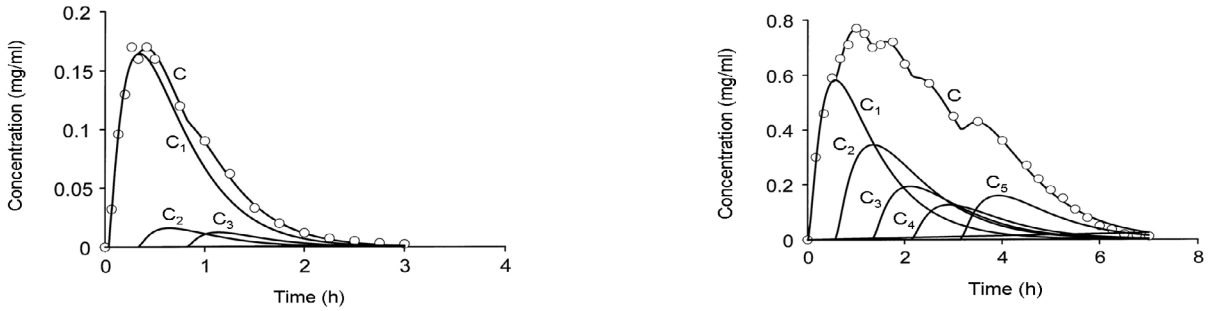


Figure 5. Relationship between AUC and G parameters depending on four oral ethanol doses. 5a) AUC - area under curve; circles and solid line - calculated AUC values and model in the form of quadratic parabola; 5b) G - gain of the whole body; circles and solid line - calculated G values and model in the form of regression line.

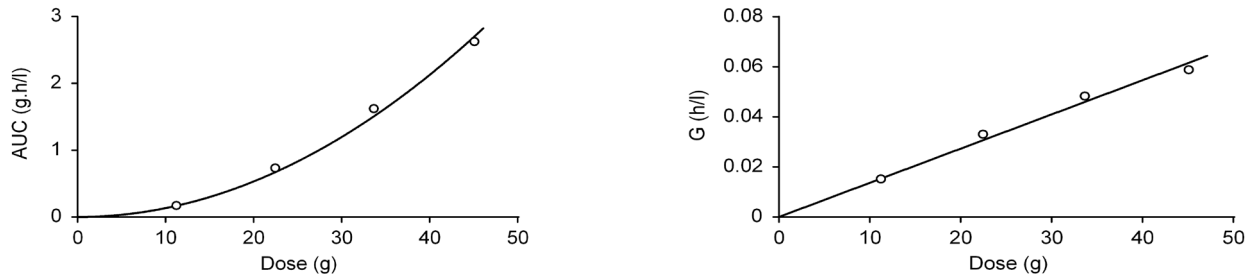


Figure 6. Relationship between MRT parameter depending on four oral ethanol doses. MRT - mean residence time; circles, squares and triangles - calculated MRT_w, MRT_{GI} and MRT_{circ} values; solid line, dashed line and dotted line - model in the form of regression line; MRT_w - mean residence time of the whole body; MRT_{GI} - mean residence time of gastrointestinal subsystem; MRT_{circ} - mean residence time of circulatory system.

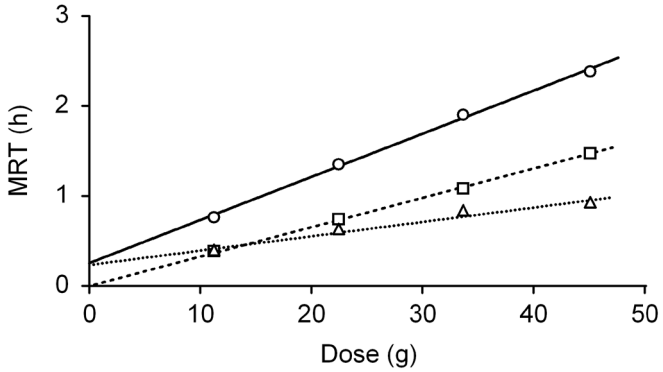


TABLE 1: Characteristics of rate constants of absorption and elimination according to different oral ethanol doses. ka1 and ka2 - rate constants of absorption of AS1 and AS2; ke- rate constant of elimination; ke* - rate constant of elimination according to Wilkinson et al. [2]; ke - rate constant of elimination estimated from the measured r-points in the terminal phase of ethanol concentration-time profile**

Dose	ka1	ka2	ke	ke*	ke**	r
(g)	(1/h)	(1/h)	(1/h)	(1/h)	(1/h)	
11.2	3.627	3.633	1.703	3.3	1.68	6
22.4	3.471	2.021	1.157	1.09	1.21	3
33.6	3.439	1.715	0.997	0.514	1.8	3
45	3.075	1.616	0.863	0.293	1.02	3

consequently to model of the first pass effect of ethanol through gastrointestinal tract. Contrary to the study of Wilkinson et al. [2], our structural model does not use Michaelis-Menten elimination kinetics (Fig.2) and does not consider the maximum velocity Vm, Michaelis constant Km and total body water V in the structure.

The Wilkinson's model assumed a little absorption from the stomach and the alcohol dose was rapidly absorbed in the intestine. The rate of gastric emptying was a postulated but not demonstrated feed-back mechanism; some of the alcohol was absorbed from the stomach directly but was not included in this model [2]. However our structural model includes the assumption of ethanol absorption from both the stomach and the small intestine, directly to the blood circulation. Many authors aimed to study of percentage of absorbed ethanol from the stomach. Following Levitt et al. [11], the absorption of the ethanol from the stomach is 10%, and 28% with the meal, respectively. It seems to be a contradiction to the finding of Cortot et al. [12] that about 70% of the ethanol ingested with a meal is absorbed from the stomach after the oral administration of 6.7 times higher dose of ethanol. This also supports our results that the higher dose is absorbed from the stomach rather than from the small intestine. Holt [13] indicates that ethanol can be absorbed from the stomach up to 43%. Marco and Kelen [14], Eckardt et al. [15] and Smith et al. [16] claim that 80% of the ethanol is emptied into the small intestine. This suggests the fact confirmed by the Haseba et al. [17] study with mice that changes of elimination kinetics of ethanol depending on approach and density of administered doses. According to results obtained with our physiologically-motivated structural model, 85.2%, 49.2%, 44.1% and 35.5% of absorbed ethanol after the oral administration of 11.2g, 22.4g, 33.6g and 45g doses of absolute ethanol, respectively, were from the stomach (Fig. 3a). These results point to extremely fast ethanol absorption from the stomach beginning with its early residence (Fig.3b, c).

The structural developed model is able to provide estimation of significant physiologically interpretable model parameters, i.e. absorbed ethanol dose fraction F, time constant of the subsystem T, and time delay of the subsystem τ. Obtained results show that the volume of the ethanol doses presented the markedly influence to the variation of the model parameters. As for ethanol dose fractions (Fig. 3a), the fraction F1 related to AS1 (i.e. stomach) for the least ethanol dose (11.2g), presents the highest fraction (85.2%) in comparison with other ethanol dose. As shown in Fig.3b, the time delays τ2 to τ5 of the fractions related to absorption site AS2 signify the proportionality with the increasing dose. This finding can show the influence of the amount of oral administered ethanol dose, as well as gastric emptying, on the start of the absorption of the fractions from the small intestine. The similar proportionality with the increasing oral ethanol dose was observed in the case of time constant parameter within the gastrointestinal tract (Fig.3c). Interpretation of the figures point to a regulation mechanism of ethanol when, in the case of the highest dose of absolute ethanol (45g), the fraction F5, related to absorption site AS2 (see Fig.3a), was absorbed with the latest time delay τ5 (see Fig.3b) and achieved the longest mean time in the absorption site AS2 (see Fig.3c).

Proposed model is able to fit multiple waves of ethanol concentration-time profiles expressing the individual dose fraction of ethanol. The shapes of these profiles after the oral administration of the ethanol doses show similarity between measured and estimated concentration profiles without significant

deviations. The illustration of multiple concentration waves after the oral administration of the lowest (11.2g) and the highest (45g) ethanol doses is depicted in Fig.4a, b.

In Table 1, it is seen that the rate constants of elimination estimated from the structural model ke, are closer to ke** value estimated from the terminal phase of ethanol concentration-time profile, than ke* estimated from the Wilkinson´s model [2] with Michaelis-Menten elimination kinetics. The parameter ke** demonstrates more stability (dose independence), than the parameter ke* that demonstrated up to threefold lower values at higher ethanol doses. Similarly, the rate constant of absorption, 25.1 h-1 according to Wilkinson et al. [2], is not in accordance with the markedly lower rate constants ka1, ka2 values listed in Table 1.

The regression functions of dependence between chosen model parameters, estimated parameters and ethanol dose were detected on the base of minimal value of Akaike's information criterion [10] and good fit of dependence between model parameters and dose in the all cases (Figs.5, 6).

As shown in Fig. 5a, the dependence of AUC on ethanol dose is parabolic, while the dependence of parameters G (Fig.5b) and MRT on the dose (Fig.6) is linear. This relationship indicates an underlying system that is markedly nonlinear because for a linear system the AUC dependency on dose presents a linear increase and G, MRT values are constants. From this viewpoint presented physiologically-motivated structural model is a linearized model of the nonlinear system defined only for administered ethanol doses values.

Conclusions

The presented results indicate significant increasing of ethanol mean residence time in the body and increasing of the absorbed fraction number in connection with the increase in ethanol dose. The regression dependences in this work suggest that the overall picture about nonlinearity of the system of alcohol elimination from the human body is possible to obtain only by the study of dependence of observed parameters on the individual ethanol doses. The developed model presents a useful linearization based on physiologically understood parameters of the complex nonlinear ethanol metabolism.

Acknowledgments

This publication was supported by Competence Center for SMART Technologies for Electronics and Informatics Systems and Services, ITMS 26240220072, funded by the Research & Development Operational Programme from the ERDF, and Scientific Grant Agency VEGA (Bratislava), grant No. 1/0120/12.

Conflict Of Interest

The authors declare any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within that could inappropriately influence (bias) their work.

References

[1]. National Institute on Alcohol Abuse and Alcoholism (1997) Alcohol Alert: Alcohol Metabolism, No. 35, PH 371, BethesdaMD, The Institute.
[2]. Wilkinson PK, Sedman AJ, Sakmar E, Kay DR, Wagner JG (1977) Pharmacokinetics of ethanol after oral administration in the fasting state. J Pharmacokinet Biop 5(3): 207-224.
[3]. Gubala W, Zubala D (2003) Gender differences in the pharmacokinetics of ethanol in saliva and blood after oral ingestion. Pol J Pharmacol 55: 639-644.
[4]. Loizou GD, Spendiff M (2004) A human PBPK model for ethanol describing inhibition of gastric motility. J Mol Histol 35: 687-696.
[5]. Umulis DM, Gürmen NM, Singh P, Fogler HS (2005) A physiologically based model for ethanol and acetaldehyde metabolism in human beings. Alcohol 35: 3-12.
[6]. Coulter CV, Isbister GK, Duffull SB (2011) The pharmacokinetics of methanol in the presence of ethanol. Clin Pharmacokinet 50(4): 245-251.
[7]. Dedík L, Tvrdoňová M, Ďurišová M, Penesová A, Miklovičová D, Kozlovský M (2009) Computer controlled sequential simulation method: Reconsidering evaluation of measurements from frequently sampled intravenous glucose tolerance test. Comput Meth Programs Biomed 95(1): 1-9.
[8]. Tvrdonova M, Dedik L, Mircioiu C, Miklovicova D, Durisova M (2008) Physiologically motivated time-delay model to account for mechanisms underlying enterohepatic circulation of piroxicam in human beings. Basic Clin Pharmacol Toxicol 104: 35-42.
[9]. Chrenova J, Durisova M, Mircioiu C, Dedik L (2010) Effect of gastric emptying and entero-hepatic circulation on bioequivalence assessment of ranitidine. Methods Find Exp Clin Pharmacol 32(6): 413-419.
[10]. Akaike H (1976) Canonical correlation analysis of time series and the use of an information criterion. System Identification, Academic Press, New York.
[11]. Levitt MD, Li R, DeMaster EG, Elson M, Furne J, Levitt DG (1997) Use of measurements of ethanol absorption from stomach and intestine to assess human ethanol metabolism. Am J Physiol 273(36): G951-G957.
[12]. Cortot A, Jobin G, Ducrot F, Aymes C, Giraudeaux V, Modigliani R (1986) Gastric emptying and gastrointestinal absorption of alcohol ingested with a meal. Dig Dis Sci 31(4): 343-348.
[13]. Holt S (1981) Observations on the relation between alcohol absorption and the rate of gastric emptying. Can Med Assoc 124(3): 267-277, 297.
[14]. Marco CA, Kelen GD (1990) Acute intoxication. Emerg Med Clin North Am 8(4): 731-748.
[15]. Eckardt MJ, File SE, Gessa GL, Grant KA, Guerri C, Hoffman PL, Kalant H, Koob GF, Li TK, Tabakoff B (1998) Effects of moderate alcohol consumption on the central nervous system. Alcohol Clin Exp Res 22(5): 998-1040.
[16]. Smith T, DeMaster EG, Furne JK, Springfield J, Levitt MD (1992) First-pass gastric mucosal metabolism of ethanol is negligible in the rat. J Clin Invest 89(6): 1801-1806.
[17]. Haseba T, Kameyama K, Mashimo K, Ohno Y (2012) Dose-dependent change in elimination kinetics of ethanol due to shift of dominant metabolizing enzyme from ADH 1 (Class I) to ADH 3 (Class III) in mouse. Int J Hepatol Volume 2012, Article ID 408190, 8 pages, doi: 10.1155/2012/408190.