Development of the mechanistic-circulatory model to identification of deep compartment after intravenous administration of ethanol

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ABSTRACT

The work presents the systems approach to solve some of problems with pharmacokinetics modeling of ethanol after its intravenous infusion. The ethanol doses at 0.13 and 0.26 g/kg were administered via the cephalic vein to healthy mongrel dogs with measurement in femoral artery and saphenous vein, a branch of femoral vein. The development model of capillary and deep compartments of ethanol behavior, as the part of mechanistic-circulatory structural model, was developed. The development model indicates the possibility of using of ethanol concentration measurements in femoral vein for identification of deep compartment parameters, such as mean residence time of ethanol or percentage of blood flow in this compartment from the blood flow via femoral vein. The mechanistic-circulatory model structure considers also time delay for detection of ethanol time disposition and identification of deep compartments structure from the viewpoint of physiologically based pharmacokinetics model.

Key words: alcohol, blood flow, computer modelling, pharmacokinetics

1 INTRODUCTION

The aim of our work constitutes the systematic approach to solve problems related to pharmacokinetics modeling of ethanol after its intravenous infusion via the cephalic vein to dogs measured in the femoral artery and femoral vein, described in the study of Rheingold et al. (1981) Rheingold's physiologically based pharmacokinetic model according to Michaelis-Menten elimination kinetics is in the form of the set of differential equations describing the circulatory system and modeling of the concentrations in the femoral artery and femoral vein, in the deep compartment, the capillary compartment (*i.e.* peripheral capillaries) and the liver. The mean measured concentration-time profiles in femoral artery (squares) and femoral vein (triangles) following the intravenous infusion of 0.26 g/kg ethanol via the cephalic vein are shown in Fig. 1.

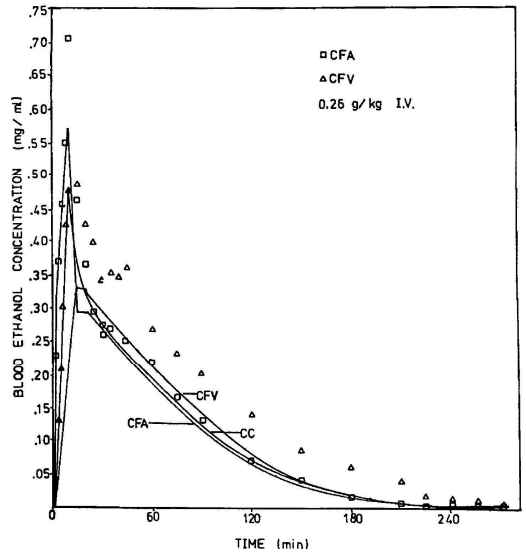

Fig. 1 Observed data and model-predicted mean blood ethanol concentrations after the constant rate intravenous infusion of ethanol of 0.26 g/kg via the cephalic vein to three dogs. Squares and triangles - mean measured ethanol concentration in femoral artery and femoral vein, respectively; lines - the model of concentration-time profile. Adapted from Jay L. Rheingold, Richard E. Lindstrom, and Paul K. Wilkinson, A new blood-flow pharmacokinetic model for ethanol, Journal of Pharmacokinetics and Biopharmaceutics 9(3), pp. 261-278, Fig. 1(c), copyright 1981, with permission of Plenum Publishing Corporation.

Unlike the Rheingold's model, our work is based on the hypothesis of the identification of deep and capillary compartments by the principle of flow well-stirred compartment model however without considering of Michaelis-Menten elimination ethanol kinetics.

With regard to the results of the work of Rheingold et al. (Rheingold et al. 1981), one needs to respond to following questions: 1) How is the contribution of measurements of concentrations in femoral vein being used for identifying the structure of the deep compartment? 2) Is it sufficient to model only one deep compartment or should consider more deep compartments with respect to related skeleton muscle groups? 3) What is the role of time delay in the model structure?

2 METHODS

2.1 Animals

Briefly, three healthy full-grown mongrel dogs (weight: 18-31 kg) participated in the study of Rheingold et al (1981). Ethanol was administered by constant infusion rate of 10 min via the cephalic vein (*vena*

cephalica) at 0.13 and 0.26 g/kg. Blood samples were collected by an indwelling catheter in the femoral artery (*arteria femoralis*) and by an additional catheter within the saphenous vein (*vena saphena magna*), a branch of the femoral vein (*vena femoralis*). Fifty microliter blood samples for ethyl alcohol were analyzed by the head-space gas chromatographic procedure on a Hewlitt-Packard[5] 5750-B Research Chromatograph equipped with a hydrogen flame ionization detector (Rheingold et al. 1981).

2.2 Prototyping model

The physiologically based model of the system describing the change of the measured ethanol concentration-time profile in femoral artery to the measured concentration-time profile in femoral vein caused by the deep (PD) and the capillary (PC) compartment of dog`s hind leg is presented as a prototyping model of the all other deep and capillary compartments. This model with the measured concentration-time profile in femoral artery C_{FA} and femoral vein C_{FV} in the input and in the output, respectively, is expressed by following equation

$$C_{FV}(s) = \left(\frac{g_{PD}}{T_{PD}.s + 1} + g_{PC} \right).C_{FA}(s) \quad (1)$$

where s is the Laplace operator, g_{PD} and T_{PD} are attenuation and mean residence time of prototyping deep compartment, respectively, and g_{PC} is attenuation of prototyping capillary compartment.

Generally, the attenuation g_P of the prototyping subsystem, as dimensionless value, is defined as

$$g_P = 1 - \frac{Cl_P}{Q_P} \leq 1 \quad (2)$$

where Cl_P and Q_P are clearance and blood flow, respectively, related to the subsystem FA-FV.

For the prototyping model it is valid that

$$g_P = g_{PD} + g_{PC} \quad (3)$$

2.3 Mechanistic-circulatory model

The general physiologically based model of a well-stirred flow subsystem with the time delay, and characterized by ethanol amounts per time unit (mg/min) as input M_{in} and output M_{out}, is expressed as

$$M_{out}(s) = \frac{G}{T.s + 1} e^{-\tau s}.M_{in}(s) \quad (4)$$

where M_{in} means M_{RA} for subsystem CP, and M_{LV} for subsystems O, OD, OC, PD, PC. M_{out} means M_{LV} for subsystem CP, and M_O, M_{OD}, M_{OC}, M_{PD} and M_{PC} for subsystems O, OD, OC, PD and PC, respectively (see Fig. 2). T is mean residence time of the individual subsystem, instead of international acronym MRT.

Parameter G, a dimensionless value, is the gain of the subsystem and can be expressed as:

$$G = \frac{Q}{Q_{CP}}.g \quad (5)$$

or

$$G = \frac{Q - Cl}{Q_{CP}} \quad (6)$$

where g, τ, Cl and Q are attenuation, time delay, clearance and blood flow, respectively, related to the individual subsystem, and Q_{CP} is blood flow through cardiopulmonary subsystem CP.

Mean residence time of ethanol in deep compartment T, can be described as:

$$T = \frac{V}{Q} \quad (7)$$

where V is the hypothetical volume of the subsystem.

Consequently, the mechanistic-circulatory model including the part with the prototyping deep compartment (PD) and the prototyping capillary compartment (PC) was developed. This model presents the model of the whole dog`s body after the ethanol administration by short infusion (I) as the input to the system, and simultaneous measurement of ethanol concentration in femoral artery C_{FA} and femoral vein C_{FV} as the outputs from the system (Fig. 2).

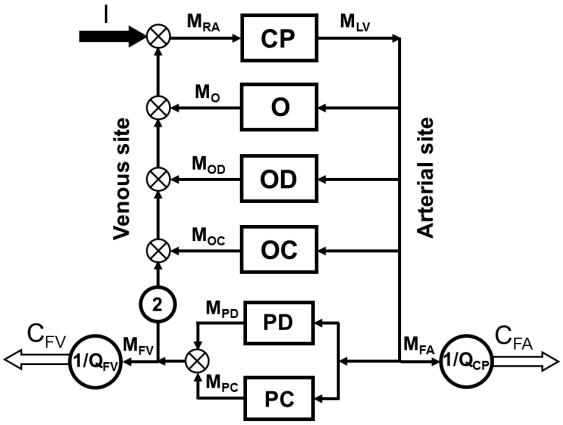

Fig. 2 Mechanistic-circulatory model including the prototyping part of the deep compartment (PD) and the capillary compartment (PC). I - input in the form of short infusion; CP - cardiopulmonary subsystem; O - other subsystem; OD - other deep compartment; OC - other capillary compartment; PD - prototyping deep compartment; PC - prototyping capillary compartment; M - ethanol amount per time unit; RA - right atrium; Q - blood flow; LV - left ventricle; C_{FA} and C_{FV} - measured concentration-time profiles of ethanol in femoral artery and femoral vein, respectively.

The modeling of the paired organs is expressed by number 2 (Fig. 2). The similar model structure included the cardiopulmonary subsystem (CP), the other subsystem (O) (*e.g.* brain, liver, kidney, stomach and intestines), the other deep compartment (OD) and the other capillary compartment (OC) in the other skeleton muscles is also assumed.

The structure of ethanol mechanistic-circulatory model with the prototyping part is expressed by the following equations:

$$M_{RA} = I + M_O + M_{OD} + M_{OC} + 2.M_{FV} \quad (8)$$

$$M_{LV}(s) = \frac{1}{T_{CP}.s+1}.M_{RA}(s) \quad (9)$$

$$M_O(s) = \frac{G_O}{T_O.s+1}.M_{LV}(s) \quad (10)$$

$$M_{OD}(s) = \frac{G_{OD}}{T_{OD}.s+1}e^{-\tau_{OD}s}.M_{LV}(s) \quad (11)$$

$$M_{OC}(s) = \frac{G_{OC}}{T_{OC}.s+1}.M_{LV}(s) \quad (12)$$

$$M_{PD}(s) = \frac{G_{PD}}{T_{PD}.s+1}e^{-\tau_{PD}s}.M_{LV}(s) \quad (13)$$

$$M_{PC}(s) = \frac{G_{PC}}{T_{PC}.s+1}.M_{LV}(s) \quad (14)$$

$$M_{FV} = M_{PD} + M_{PC} \quad (15)$$

$$C_{FV} = \frac{M_{FV}}{Q_{FV}} \quad (16)$$

If $M_{FA} = M_{LV}$ then is valid that $C_{FA} = \frac{M_{LV}}{Q_{CP}}$ (17)

where I is ethanol input in the form of a short infusion, M is ethanol amount per time unit, RA is right atrium, LV is left ventricle, O is other subsystem, CP is cardiopulmonary subsystem, FA is femoral artery, FV is femoral vein, C is measured ethanol blood concentration and Q_{CP} is blood flow through cardiopulmonary subsystem.

Regarding the mechanistic-circulatory model it is considered that the input function $I(t)$ is in the form of short infusion and infusion rate of ethanol IR is described by equation:

$$IR = \frac{Dose}{t_{\Omega}} \quad (18)$$

where t_{Ω} is the duration of ethanol infusion of 3.172 and 6.344 g/min related to 0.13 and 0.26 g/kg of ethanol dose, respectively, via the cephalic vein.

In terms of $I(t)$, in the case of $t \le 0$ and $t > t_{\Omega}$, then it is valid that $I(t) = 0$. If $0 < t \le t_{\Omega}$, then $I(t) = IR$. (19)

2.4 Parameter estimation

To estimate the model parameters, the Monte Carlo method (Manno 1999) implemented in the CCSS method (Computer Controlled Sequential Simulation) (Ďurišová & Dedík 2005, Dedík et al. 2009).

Using the parameters of the prototyping model and the mechanistic-circulatory model (Fig. 2), the vectors λ_P and λ_C were determinated.

The estimation of vector λ_P related to the prototyping model is given as

$$\lambda_P = (g_{PD}, g_{PC}, T_{PD}) \quad (20)$$

The estimation of vector λ_C related to the mechanistic-circulatory model is given as

$$\lambda_C = (Q_{CP}, Q_{FV}, G_O, G_{OD}, G_{OC}, G_{PD}, G_{PC}, T_{CP}, T_O, T_{OD}, T_{OC}, T_{PD}, T_{PC}, \tau_{OD}, \tau_{PD}) \quad (21)$$

The structure of the parameter`s vectors λ_P and λ_C were detected on the basis of the minimal value of Akaike's information criterion (Akaike 1976)

3 RESULTS

The average ethanol concentration data after the intravenous infusion of two different ethanol doses to three healthy full-grown mongrel dogs published in the study of Rheingold et al. (1981) were processed by mechanistic-circulatory model containing the prototyping part of the deep compartment (PD) and the capillary compartment (PC) (Fig. 2). The structure of the prototyping part of the deep and the capillary compartments system of one dog`s hind leg was modeled by the prototyping model with the input ethanol concentration-time profile measured in femoral artery and the output ethanol concentration-time profile measured in femoral vein. Comparable parameters estimated from parameters of prototyping and mechanistic-circulatory models for ethanol doses at 0.13 and 0.26 g/kg are listed in Table 1.

Table 1 Summary of the point estimates related to deep compartment (PD), cardiopulmonary subsystem (CP), other subsystem (O), and clearance Cl from the viewpoint of prototyping and mechanistic-circulatory models

Ethanol dose (g/kg)	Model	Deep compartment		Cardiopulm. subs.	Femoral vein	Other subs.	Clearance	
		% Q_{PD} of Q_{FV}	T_{PD} (min)	Q_{CP} (l/min)	Q_{FV} (l/min)	Q_O (l/min)	Cl_M (l/min)	Cl_∞ (l/min)
0.13	Prototyping	61.49	3.518	-	-	-	-	-
	Mechanistic-circulatory	52.50	$3.518_{const.}$	2.748	0.170	2.057	0.357	0.292
0.26	Prototyping	56.22	14.489	-	-	-	-	-
	Mechanistic-circulatory	49.07	$14.489_{const.}$	3.142	0.107	2.231	0.175	0.203

PD - prototyping deep compartment; T_{PD} - mean residence time of ethanol in prototyping deep compartment; index const. - constant value T_{PD} used from prototyping model to mechanistic-circulatory model; Q - blood flow; indices CP, FV and O - cardiopulmonary subsystem, femoral vein and other subsystem, respectively; Cl_M - the whole body clearance calculated by parameters of mechanistic-circulatory model; Cl_∞ - numerically calculated clearance by Dose/$AUC_{\infty FV}$.

The calculation of the whole body clearance Cl_M by model parameters of the mechanistic-circulatory model uses the following equation:

$$Cl_M = Q_{CP} - Q_O.g_O - Q_{OD}.g_{OD} - Q_{OC}.g_{OC} - 2.(Q_{PD}.g_{PD} + Q_{PC}.g_{PC}) \quad (22)$$

where for attenuation g of the subsystem according to Equation (5) is valid

$$g = G\frac{Q_{CP}}{Q} \quad (23)$$

where G is gain of the subsystem, Q is blood flow of the subsystem, indices CP, O, OD, OC, PD and PC mean cardiopulmonary subsystem, other subsystem, other deep compartment, other capillary compartment, prototyping deep compartment and prototyping capillary compartment, respectively. Number 2 expresses the modeling of the paired organs.

The average blood ethanol concentration-time profiles in the femoral artery (circles and thick solid line) and the femoral vein (squares and thin solid line) after the intravenous infusion of 0.13 and 0.26 g/kg of ethanol over 10 min via the cephalic vein in three dogs, fitting by the mechanistic-circulatory model included the prototyping part of the deep and the capillary compartment, are showed in Figs. 3 and 4, respectively.

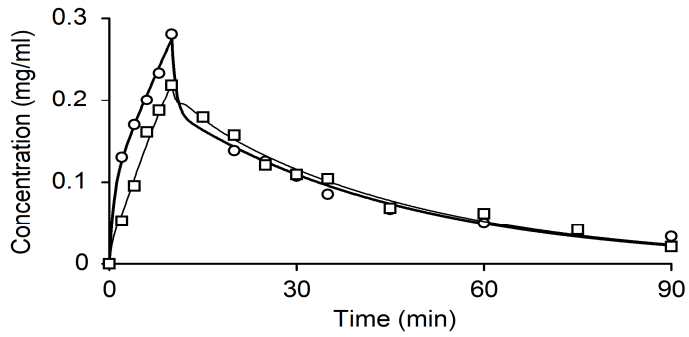

Fig. 3 Mean blood ethanol concentration-time profiles in femoral artery and femoral vein after the intravenous infusion of 0.13 g/kg of ethanol by mechanistic-circulatory model. Circles and thick solid line - mean measured concentration and the model of concentration-time profile, respectively, related to femoral artery; squares and thin solid line - mean measured concentration and the model of concentration-time profile, respectively, related to femoral vein.

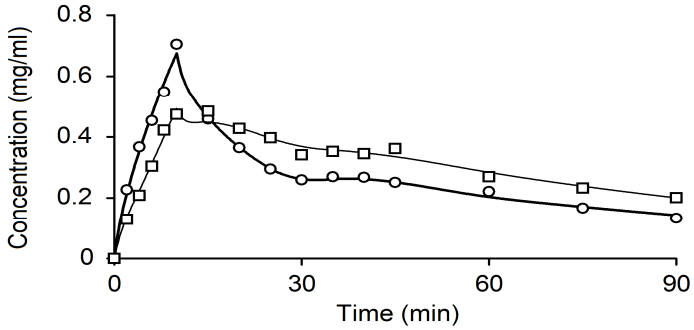

Fig. 4 Mean blood ethanol concentration-time profiles in femoral artery and femoral vein after the intravenous infusion of 0.26 g/kg of ethanol by mechanistic-circulatory model. Circles and thick solid line - mean measured concentration and the model of concentration-time profile, respectively, related to femoral artery; squares and thin solid line - mean measured concentration and the model of concentration-time profile, respectively, related to femoral vein.

Table 2 contains the values of the estimated parameters of the mechanistic-circulatory model corresponding with Figs 3 and 4.

Table 2 Summary of the point estimates from the viewpoint of mechanistic-circulatory model including prototyping part of deep and capillary compartments

Ethano dose /kg)	Other deep comp.			Other capillary comp.	Prototyping deep comp.			Prototyping ıpillary comp.
	τ_{OD} (min)	G_{OD} (-)	T_{OD} (min)	G_{OC} (-)	τ_{PD} (min)	G_{PD} (-)	T_{PD} (min)	G_{PC} (-)
0.13	-	-	-	-	1.525	0.032	3.518	0.029
0.26	24.079	0.047	2.410	0.102	3.652	0.021	14.489	0.022

τ - time delay of the subsystem; G - gain of the subsystem; T - mean residence time of the subsystem; τ_{OD}, G_{OD}, T_{OD} - model parameters related to the other deep compartment; G_{OC} - model parameter related to the other capillary compartment; τ_{PD}, G_{PD}, T_{PD} - model parameters related to the prototyping deep compartment; G_{PC} - model parameter related to the prototyping capillary compartment.

The average blood ethanol concentration-time profiles in the femoral vein C_{FV} related to specific deep (thick solid line) and capillary compartment (thin solid line) after intravenous infusion of 0.13 g/kg and 0.26 g/kg of ethanol fitted by prototyping model is shown in Figs 5 and 6, respectively. The input to the system presents the ethanol concentration-time profile measured in femoral artery.

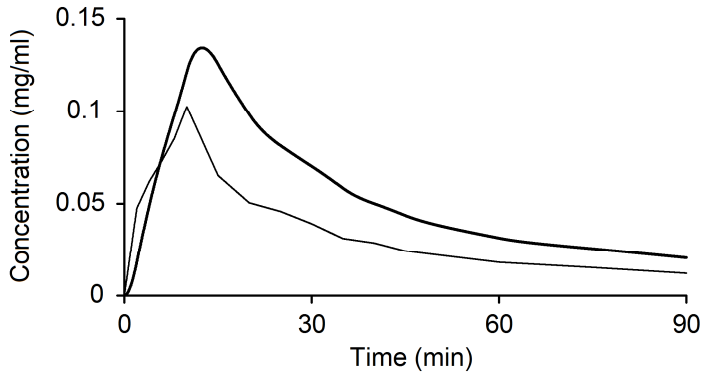

Fig. 5 Mean blood ethanol concentration-time profiles in femoral vein C_{FV} of deep compartment (PD) and capillary compartment (PC) after the intravenous infusion of 0.13 g/kg of ethanol, fitted by prototyping model. Thick solid line - the model of concentration-time profile related to prototyping deep compartment (PD); thin solid line - the model of concentration-time profile related to prototyping capillary compartment (PC).

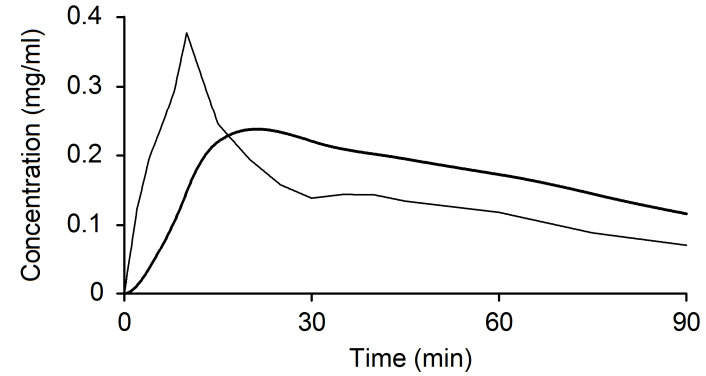

Fig. 6 Mean blood ethanol concentration-time profiles in femoral vein C_{FV} of deep compartment (PD) and capillary compartment (PC) after the intravenous infusion of 0.26 g/kg of ethanol, fitted by prototyping model. Thick solid line - the model of concentration-time profile related to prototyping deep compartment (PD); thin solid line - the model of concentration-time profile related to prototyping capillary compartment (PC).

4 DISCUSSION

The model developed by Rheingold et al. (1981) contains the liver compartment; the peripheral circulation compartment including femoral artery, peripheral capillaries and femoral vein; and the deep compartment. This model was elaborated for ethanol in the dog, and was based on blood and tissues volumes and blood flows taken from average values reported in the previous literature. Moreover, the maximum reaction rate V_m, Michaelis constant K_m and distributional rate constants K_{13}, K_{31}, as the parameters, were determined by the fitting of the input blood ethanol concentration-time data. Contrary to the model by Rheingold et al. (1981), our well-stirred flow compartment model does not use Michaelis-Menten elimination kinetics and does not consider any blood volume V, the maximum reaction rate V_m nor the Michaelis constant K_m. However, the time delay parameter is considered in our model structure. While Rheingold's model includes microcirculation between the deep and the capillary compartments, our mechanistic-circulatory model considers parallel connection of these compartments between arterial and venous site because of the better Akaike's information criterion value (1976) related to this model, in comparison with the competitive model including microcirculation.

The main indicators of the effect of two intravenous administrated ethanol doses (0.13 and 0.26 g/kg) on physiological parameters of dogs by prototyping and mechanistic-circulatory models are listed in Table 1. By this table, the blood flow via cardiopulmonary subsystem Q_{CP}, estimated by the mechanistic-circulatory model including the prototyping part of the deep and the capillary compartment, shows approximately 12% decline at 0.13 g/kg (2.748 l/min) compared to 0.26 g/kg (3.142 l/min) ethanol dose. Our presented observations are not in contradiction with the results in previous literature. Several previous studies were aimed to study regional blood flow distribution in dogs in the resting level or during exercise (Werner & Horvath 1952, Van Citers & Franklin 1969, Alyono et al. 1986). According to the study of Ishii et al. (1973), the mean cardiac output at healthy anesthetized mongrel dogs (weight: 15-30 kg), using the special method with distributed ^{43}K in the myocardium and scintillation camera, was 3.08 ± 0.35 l/min. A similar mean value of cardiac output, 3.2 ± 1.1 l/min, was detected for twelve healthy dogs (weight: 15-34 kg) in the study of Shih et al. (2011). Critchley et al. (2005) observed the mean cardiac output in six anesthetized male dogs (weight: 11-22 kg) of 2.60 ± 0.99 l/min and 2.62 ± 1.04 l/min, measured by aortic flowprobe with a high-precision four-crystal array and by the ultrasonic cardiac output monitor (USCOM). Following the intravenous (IV) bolus administration at 1.5 g/kg ethanol in 5% dextrose in water solution (D5W) over 20 min to anesthetized dogs (mean weight: 18.8 ± 2.5 kg), Wilson et al. (2009) detected mean value of cardiac output at 1.6 l/min. After the combined IV bolus administration of ethanol (1.5 g/kg in D5W) plus 7.5 mg/kg cocaine hydrochloride in 0.9% normal saline, it was observed non-significant decrease in cardiac output and moderate increase in myocardial function and blood flow due to cocaine were attenuated by ethanol (Wilson et al. 2001, 2009).

The blood flow via the other subsystem Q_O (included liver, kidney, stomach etc.) shows approximately 7% decline at 0.13 g/kg (2.057 l/min) compared to 0.26 g/kg ethanol dose (2.231 l/min). Regarding the percentage of blood flow via a deep compartment Q_{PD} in relation to the whole blood flow via femoral vein Q_{FV}, both prototyping and mechanistic-circulatory models indicate about 7% increase at 0.13 g/kg (61.49% and 52.50%) compared to 0.26 g/kg ethanol dose (56.22% and 49.07%). In the case of mechanistic-circulatory model, the percentage of blood flow Q_{PD} was detected at constant value of ethanol mean residence time in deep compartment T_{PD} from the prototyping model. The presented T_{PD} parameter shows significantly lower value at 0.13 g/kg ethanol dose (3.518 min) in comparison with higher dose (14.489 min). The whole body clearance Cl_M calculated by the parameters of the mechanistic-circulatory model increased about 50% at 0.13 g/kg (0.357 l/min) compared to 0.26 g/kg ethanol dose (0.175 l/min) (Table 1).

The estimation of the clearance $Cl_{M,}$ is comparable with the numerically calculated clearance $Cl_{\infty} = \frac{Dose}{AUC_{\infty FV}}$ by the ethanol dose and area under measured concentration curve of femoral vein $AUC_{\infty FV}$ interpolated from zero to infinity, where the values 0.292 and 0.203 l/min for 0.13 and 0.26 g/kg ethanol doses, respectively, were calculated.

Table 2 indicates that in the case of ethanol dose 0.13 g/kg, the model parameters τ_{OD}, G_{OD}, T_{OD} related to the other deep compartment and G_{OC} related to the other capillary compartment are marked by dash ("-"), while in the case of 0.26 g/kg are listed by values. This reflects that for ethanol dose 0.13 g/kg, because of the better Akaike's information criterion value (-80.6), the mechanistic-circulatory model without other deep compartment (OD) and other capillary compartment (OC) was chosen, in comparison with the competitive model including these compartments in the structure (-72.6). From this viewpoint we conclude that for 0.13 g/kg of ethanol dose, the significant influence to the concentration-time ethanol profile presented mainly the circulation within the dog`s hind legs, while the influence of the other skeleton muscles was non-identified. On the other hand, for 0.26 g/kg of ethanol dose other skeleton muscles also played an important role.

Consequently, the model results indicate the sensitivity of the developed prototyping and mechanistic-circulatory models of ethanol behavior in the dog`s body after intravenous infusion of two different ethanol doses, and with sufficient identification of deep and capillary compartments by mathematical consideration different than the viewpoint of Michaelis-Menten elimination ethanol kinetics.

5 CONCLUSION

The summary of parameter estimation results according to the prototyping and the mechanistic-circulatory models can help to answer the questions listed in the beginning of this work as follows:

1) The developed prototyping model indicates the possibility of using of ethanol concentration measurements in femoral vein for identification of parameters and properties of the deep compartment, as mean residence time of ethanol or percentage of blood flow in this compartment from the whole blood flow via femoral vein.

2) The proposed mechanistic-circulatory model including the prototyping part of deep and capillary compartment, with measured ethanol concentration in the femoral vein and the femoral artery related to one leg, but with the assumption for two identical dog`s hind legs, is considered. The similar structure of this model with the other deep and the other capillary compartments respecting the other related skeleton muscles is assumed, as well. However, for 0.13 g/kg of ethanol dose, the important influence to the concentration-time ethanol profile presents from the dog`s hind legs, while for 0.26 g/kg of ethanol dose plays an important role also from the other skeleton muscles.

3) In contrast to the Rheingold's model, the structure of our developed mechanistic-circulatory model considers a time delay in the prototyping deep compartment and in the other deep compartment. The estimation of time delay parameter plays a significant role in detection of the time disposition of ethanol for its input to these compartments and consequently for the identification of deep compartments structure within the whole model from the viewpoint of physiologically interpreted parameters.

Compared to Rheingold's physiologically based pharmacokinetic model with Michaelis-Menten elimination kinetics (Rheingold et al. 1981), our mechanistic-circulatory model can be potentially useful in the development of novel approaches to the pharmacokinetic modeling of the behavior of ethanol after the intravenous infusion in dogs, with potential correlations to human.

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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. Akaike, H. (1976). Canonical correlation analysis of time series and the use of an information criterion. System Identification. New York: Academic Press.
2. Alyono, D., Anderson, R.W., Parrish, D.G., Dai, X.Z., Bache, R.J. (1986). Alterations of myocardial blood flow associated with experimental canine left ventricular hypertrophy secondary to valvular aortic stenosis. *Circ. Res,* 58, 47-57.
3. Critchley, L.A., Peng, Z.Y., Fok, B.S., Lee, A., Phillips, R.A. (2005). Testing the reliability of a new ultrasonic cardiac output monitor, the USCOM, by using aortic flowprobes in anesthetized dogs. *Anesth. Analg.*, 163, 748-53.
4. 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. Prog. Bio.,* 95**,** 1-9.
5. Ďurišová, M., Dedík, L. (2005). New mathematical methods in pharmacokinetic modeling. *Basic Clin. Pharmacol. Toxicol.,* 96, 335-42.
6. Ishii, Y., MacIntyre, W.J., Pritchard, W.H, Eckstein, R.W. (1973). Measurement of total myocardial blood flow in dogs with ^{43}K and the scintillation camera. *Circ. Res.,* XXXIII, 113-22.
7. Manno, I. (1999). Introduction to the Monte – Carlo Method. Budapest: Akademiai Kiado.
8. Rheingold, J.L., Lindstrom, R.E., Wilkinson, P.K. (1981). A new blood-flow pharmacokinetic model for ethanol. *J. Pharmacokinet. Biop.,* 9, 261-78.
9. Shih, A., Giguère, S., Vigani, A., Shih, R., Thuramalla, N., Bandt, C. (2011). Determination of cardiac output by ultrasound velocity dilution in normovolemia and hypovolemia in dogs. *Vet. Anaesth. Analg.,* 38, 279-85.
10. Van Citters, R.L., Franklin, D.L. (1952). Cardiovascular performance of Alaska sled dogs during exercise. *Circ. Res.,* XXIV, 33-42.
11. Werner, A.Y., Horvath, S.M. (1952). Measurement of hepatic blood flow in the dog by the bromsulphalein method. *J. Clin. Invest.,* 31, 433-9.
12. Wilson, L.D., Jeromin, J., Garvey, L., Dorbandt, A. (2001). Cocaine, Ethanol, and Cocaethylene Cardiotoxity in an Animal Model of Cocaine and Ethanol Abuse. *Acad. Emerg. Med.,* 8, 211-22.
13. Wilson, L.D., Malik, M., Willson, H. (2009). Cocaine and ethanol: combined effects on coronary artery blood flow and myocardial function in dogs. Acad. Emerg. Med., 16**,** 646-55.