

Use of pharmacokinetic modelling in back calculation of alcohol concentration

Piekoszewski W, Guba \square a W

Institute of Forensic Research, Westerplatte 9, 31-033 Kraków, Poland

Abstract

Widmark's formula is very often used for translation a measured blood alcohol concentration into the amount of alcohol consumed or a concentration of alcohol in the moment of accident. However, experimental data indicate that the Widmark calculations are uncertain for these estimations.

The aim of the study was to check the usefulness of pharmacokinetic modeling for back calculation of alcohol concentration. A group of 17 persons (12 men and 5 women) was subjected to an investigation. The persons in each experiment were given the alcohol in the form of 40% v/v vodka. The amounts of alcohol was supposed to cause the maximum concentration of 1g/L ethanol in blood according to the theoretical calculations based on the Widmark formula. The alcohol concentration in blood samples was determined by gas chromatography.

The simulations were performed using two variants of the one compartment model with first order absorption and zero order elimination. The assumptions of rate of absorption (half-life of absorption 15 and 20 min) and elimination (β_{60} 0.1 and 0.2 g/l/h) were adopted.

The maximum alcohol concentrations obtained from simulation were in the range from 0.68 to 0.84 g/l according to the adopted assumption, and these values were very close to these obtained after alcohol consumption by volunteers (0.77 ± 0.19)

The performed research shows that pharmacokinetic modeling allowed the more precise estimation of maximal alcohol concentration then Widmark formula, however the calculation of consumed dose and back calculation of alcohol concentration are similar by both method.

Keywords

Forensic toxicology, ethanol pharmacokinetics pharmacokinetic modeling, Widmark calculations

Introduction

The quantities of alcohol consumed and time of consumption are important facts, which can be obtained from a suspect who has been stopped for driving under the influence of alcohol. In many forensic cases alcohol concentration is measured some time after the accident (escape of the driver from the scene of accident). In forensic practice, the Widmark method is used [1] for retrograde extrapolation of the consumed dose of alcohol or its concentration during the accident. This method is saddled with many errors [2, 3]. Alternatively the pharmacokinetic modeling (PK) can be use for these calculations. The goal of this study was to compare results of calculation (alcohol concentration, β_{60} etc.) obtained by applying the Widmark equation and one compartment model with first order rat of absorption and zero order elimination.

Methods

Results presented in this paper were collected by the Institute of Forensic Research over the two month long experiment. Written informed consent was obtained from each subject in the

study. The volunteers (aging 27 – 49 years), twelve men and five women received a dose of 0.7 g/kg (man) and 0.6 g/kg (women) of ethanol in the form of vodka diluted with mineral water. After inserting a catheter into a large cubical vein, fifteen to twenty blood samples were taken at time intervals ranging from 5 to 380 minutes.

The ethanol concentrations were measured using headspace gas chromatography (Perkin Elmer, AutoSystem XL with HS 40 autosampler). A 0,2 ml volume of blood was mixed with 1,8 ml (0,02% g/L) 2-methylpropan-2-ol (tetra-butyl alcohol) as an internal standard (IS). The samples were placed into the autosampler. Headspace incubation time was 22 minutes at 60°C. Separation was achieved on a Carbowax 1500 column under isocratic conditions (temp. 100°C); the temperature of the flame ionization detector was 200°C. Chromatograms were recorded and calculations were done using Turbochrom computer program. Six points (0.1 – 4 g/L) standard curve was prepared {Ethanol concentration = f (AUC_{ethanol}/AUC_{IS})}

The pharmacokinetic calculations were done using first-order model of absorption and zero-order elimination. The computer program ADAPT II (Biomedical Simulations Resource, University of Southern California) was used for pharmacokinetic calculations.

The following equations were employed:

$$\frac{dC_{EtOH}}{dt} = \left(\frac{k_b \cdot D}{V} \cdot e^{-k_{ab} \cdot t} \right) - \frac{V_{Max} \cdot C_{EtOH}}{(K_M + C_{EtOH})} \quad (1)$$

and

$$\frac{dC_{EtOH}}{dt} = \left(\frac{k_b \cdot D}{V} \cdot e^{-k_{ab} \cdot t} \right) - \beta_{60} \quad (2)$$

where: k_a is absorption rate constant, β_{60} – zero order rate of elimination, D - dose of alcohol, V - apparent volume of distribution after oral dose, V_{Max} - maximum velocity of ethanol elimination, K_M - Michaelis' constant and C_{EtOH} - ethanol concentration.

In calculation also Widmark equation was apply.

$$\text{Amount of alcohol absorbed} = wV(C_t + \beta_{60}t) \quad (3)$$

were: w is body weight, C_t – alcohol concentration at time t, volume of distribution was calculated from relation Dose/ C_0 .

To calculate Widmark's coefficient, the linear regression technique was used (terminal part of concentration time curve).

Results and Discussion

In table 1, the mean values \pm SD (for whole studied group) of calculated pharmacokinetic parameters of alcohol are shown. The rate of alcohol disappearance (β_{60}) and volume of distribution were obtained from curve fitting and by dividing the dose of consumed alcohol by extrapolated concentration at time 0 (zero). The values of parameters obtained by these two methods were similar and statistically significant differences were not shown. Other estimated parameters - half time of absorption (21.7 ± 13.5 min) and volume of distribution (0.7074 ± 0.1209 or 0.7814 ± 0.1442 L/kg) - were in the same range as reported in literature

[3, 4]. However, the variability of rate of elimination is moderate (CV of β_{60} below 30%) and the intersubject changes of half time of absorption were higher than 60 %.

Table 1. Mean value of alcohol pharmacokinetic parameters in 17 subjects.

Parameter (mean \pm SD)	Pharmacokinetic modeling	Widmark calculation
V_{Max} [mmol/L/h]	6.35 ± 2.81	-
K_M [mmol/L]	4.41 ± 4.09	-
V_d [L/kg]	0.7074 ± 0.1209	0.7814 ± 0.1442
$T_{1/2a}$ [min]	21.7 ± 13.5	-
β_{60} [g/h/L]	0.164 ± 0.025	0.140 ± 0.042
C_o [g/L]	-	0.89 ± 0.150

Examples of concentration- time profiles of alcohol after consuming 0.7 g/kg alcohol as vodka by two volunteers are shown in Figure 1.

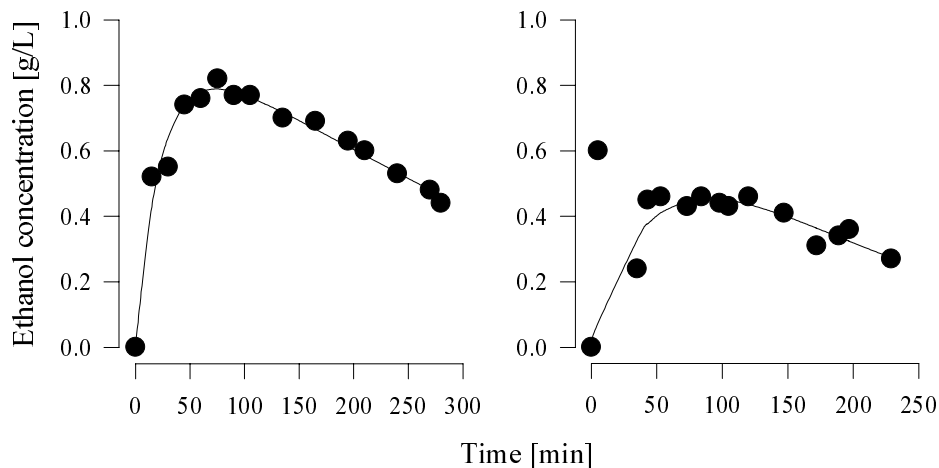


Figure 1. Two typical profiles of alcohol concentration in blood (symbols represent experimental data, and lines are the best fitting of one compartment models with first order absorption and zero order elimination to the data).

Even from this figure a big difference can be seen in the rate of absorption and maximum concentrations, which are achieved after the same dose of ethanol in standardized experimental conditions. These observations were confirmed by calculated parameters (Table 1 and 2). The parameters describing the rate of metabolism (V_{MAX} and K_M) obtained in these studies are in the same range as reported in literature [5]

Table 2. Maximum concentrations and time of maximum concentrations obtained by computer simulation, Widmark calculation and experimentally.

	Simulation				Widmark calculation	Experimental results
	Biological half-life of absorption					
	15 min		20 min			
	$\beta_{60} = 0.1$	$\beta_{60} = 0.2$	$\beta_{60} = 0.1$	$\beta_{60} = 0.2$		
C_{max} [g/L]	0.84	0.74	0.81	0.68	1.0	0.77±0.19
t_{max} [min]	75	60	90	75		64.0±20.6

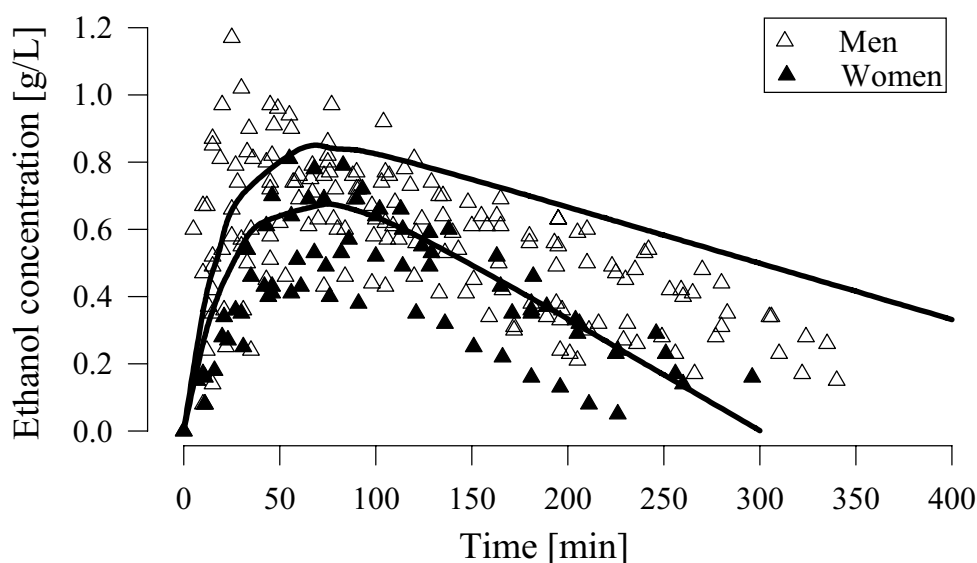


Figure 2. Experimental data (symbols) and simulated changes of alcohol concentration dependent on time after administration (lines). Upper lines t_a 15 min, β_{60} 0.1 g/L/h, lower t_a 20 min, β_{60} 0.2 g/L/h

Table 2 and Figure 2 show the maximum concentration of ethanol and time of achieving this concentration obtained by computer simulation (equations 1 and 2) and Widmark calculation with experimental data. As can be see the computer simulation (with assumption described in Methods) more precisely predicted the maximum concentration than Widmark method.

Concentration 1 g/L, predicted by Widmark calculations were observed only in 11.8 % of voluntaries while concentrations predicted by pharmacokinetic simulation were measured in 41.2 % cases (Table 3).

Table 3. Percent of blood samples dependent on maximum concentration.

Ethanol concentration	Simulation *	Widmark calculation *
Above expected [%]	23.0 (>0.84 g/L)	6.5 (>1.1 g/L)
Expected [%]	41.2 (0.68-0.84 g/L)	11.8 (0.9-1.1)
Under expected [%]	35.3 (<0.68)	81.6 (<0.9 g/L)

* In parenthesis ethanol concentrations

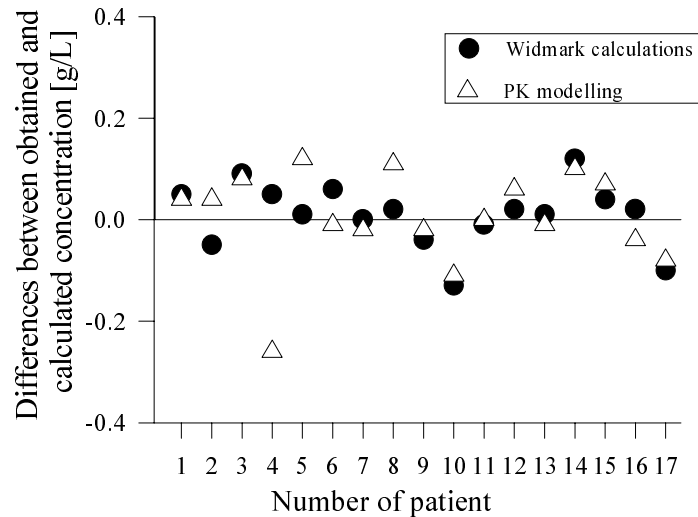


Figure 3. Comparison between the estimated (back calculated) and determined concentration of alcohol. (back calculation from time 4 h to 2 h)

These kinds of differences were not observed when both methods were used for back calculation of ethanol concentration (Figure 3)

These results confirmed that contrary to computer simulation, Widmark equation overestimates the maximal concentration of ethanol after consumption of a certain dose of alcohol. Both Widmark's equation and pharmacokinetic modeling provides a reliable way to back calculate of ethanol concentration and estimate the dose of alcohol consumed.

References.

1. Widmark EMP. Principles and Applications of Medico-legal Alcohol Determination. Biomedical Publications, Davis, CA.1981; 107-108.
2. al-Lanqawi Y., Moreland TA., McEwen J., Halliday F., Durnin CJ., Stevenson IH. Ethanol kinetics: extent of error in back extrapolation procedures. Br J Clin Pharmacol 1992; 34: 316-321.
3. Jones A.W., Hahn R.G. Pharmacokinetics of ethanol in patients with renal failure before and after hemodialysis. Forensic Sci. Inter.,1997; 90: 175-183.
4. Gullberg R.G., Jones A.W. Guidelines for estimating the amount of alcohol consumed from a single measurement of blood alcohol concentration: re-evaluation of Widmark's equation. Forensic Sci. Inter., 1994; 69: 119-130.
5. Kohlenberg-Moller K., Bitsch I. Neue Methoden zur pharmakokinetischen Bestimmung des Alkohols und seiner Metaboliten bei weiblichen und mannlichen Versuchspersonen. Blutalkohol, 1989; 26: 396-404.