Population Pharmacokinetics as a Tool to Reevaluate the Complex Disposition of Ethanol in the Fed and Fasted States

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Abstract
The pharmacokinetics (PK) of ethanol are important in pharmacology and therapeutics because of potential drug-alcohol interactions as well as in forensic science when alcohol-related crimes are investigated. The PK of ethanol have been extensively studied since the 1930s, although some issues remain unresolved, such as the significance of first-pass metabolism, whether zero-order kinetics apply, and the effects of food on bioavailability. We took advantage of nonlinear mixed-effects modeling to describe blood-alcohol concentration (BAC) profiles derived from 3 published clinical studies involving oral, intraduodenal, and intravenous administration of ethanol with and without food. The overall data set included 1510 BACs derived from 72 healthy subjects (60 men, 12 women) aged between 20 and 60 years. Two-compartment models with first-order absorption and Michaelis-Menten elimination kinetics adequately described the BAC profiles. Food intake had 2 separate effects: It reduced the absorption rate constant and accelerated the maximum elimination rate. Estimates of the maximum elimination rate (fasted) and the food effect (as a factor) were 6.31 g/h (95%CI, 6.04-6.59 g/h) and 1.39-fold (95%CI, 1.33-1.46-fold), respectively. Simulations showed that the area under the BAC-time curve (AUC) was smaller with lower input rate of ethanol, irrespective of any first-pass metabolism. The AUC from time 0 to 10 hours for a 75-kg subject was 2.34 g L/h (fed) and 3.83 g L/h (fasted) after an oral dose of 45 g ethanol. This difference was mainly attributable to the food effect on ethanol elimination and depended less on the absorption rate. Our new approach to explain the complex human PK of ethanol may help when BAC predictions are made in clinical pharmacology and forensic medicine.

Keywords
covariate analysis, ethanol, food effect, modeling and simulation, pharmacokinetics and drug metabolism, population pharmacokinetics

Ethanol (alcohol) is one of the most widely used recreational drugs in the world, and excessive drinking and drunkenness have a major impact on public health and human behavior.1,2 The pharmacokinetics (PK) of ethanol are important to understand from both theoretical and practical viewpoints, especially in forensic science and legal medicine, because many crimes are committed when people are under the influence of alcohol.

After oral intake, ethanol is rapidly and completely absorbed from the gastrointestinal tract, and the maximum blood alcohol concentration (BAC) is usually reached by 30-60 minutes after intake.3 Thereafter, absorbed ethanol is distributed into the total body water (TBW) compartment, and the average volume of distribution (Vd) for men is ≈0.7 L/kg, compared with ≈0.6 L/kg for women.4

Ethanol is presumed to undergo some first-pass metabolism in the stomach and/or the liver, with extent and relevance depending on the ingested dose, fed-fasted state, and the rate of absorption.5,6 Reported bioavailability of oral ethanol ranges between 17% and 100%.7,8

Ethanol is primarily eliminated by hepatic oxidative metabolism to acetaldehyde (>90%), mainly mediated

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by class I alcohol dehydrogenases (ADHs). The cytochrome P450 (CYP) enzyme CYP2E1 also contributes to the hepatic metabolism of ethanol to acetaldehyde, especially after periods of chronic drinking and when high BACs are reached.4,9

Less than 10% of the dose gets excreted unchanged in breath, urine, and sweat.4 There is a general consensus that overall hepatic metabolism of ethanol in humans is reflected by dose-dependent mixed-order Michaelis-Menten elimination kinetics, because the ADH enzyme is saturated at BAC >0.15-0.2 g/L.3,4 The maximum elimination rate (V_max) of ethanol is reported to reach about 8.5 g/h in a typical White adult.3

There are both inter- and intraindividual variations in rates of ethanol metabolism and other PK parameters. Respective covariates reported in the literature include sex, descriptors of body mass such as body weight (BW) or body mass index (BMI), route of ethanol administration, the dose ingested, the person’s drinking habits (habituation), and speed of drinking, as well as the intake of food.4,6,10–15 Finally, polymorphisms in the genes encoding the various ADHs and aldehyde dehydrogenases lead to different kinetic properties of the enzymes and hence to differences in the PK of ethanol.12,15

It has been known since the 1930s that drinking alcohol after a meal has a major influence on the shape of BAC profiles.16 Food intake leads to a lower peak BAC and a later occurring maximum BAC (C_max) compared with drinking the same dose on an empty stomach.6,17,18 The area under the BAC-time curve (AUC) is smaller in the fed state, and the time to eliminate the administered dose is shorter when ethanol is consumed after a meal.19–21

In the present analysis, we took advantage of non-linear mixed-effects modeling and applied this to the evaluation of BAC profiles derived from 3 published clinical studies. Our aim was to develop a population PK model for use in evaluating BAC profiles of ethanol and important covariates, with special emphasis on the effect of food intake.

We have updated the traditional method of evaluating BAC profiles, which assumes zero-order kinetics, to include a consideration of mixed-order kinetics and enzyme saturation. This new PK model of ethanol allows making quantitative estimates of the underlying PK parameters and simulation of BAC versus time profiles depending on covariates, such as mode of administration and fed versus fasted state.

Methods

Data Sets and Study Design

BAC profiles derived from 3 published clinical studies performed by Jones,22 Hahn et al,23 and Ammon et al24 were reevaluated using population PK modeling. The studies were conducted in accordance with the Declaration of Helsinki and the local regulatory and ethical requirements. Informed consent was obtained from all volunteers.

Primary data were still available for all 3 clinical trials, which allowed for the retrospective population PK analysis. The studies were performed under strictly controlled drinking conditions in a sufficiently large number of volunteers. In all studies, ethanol was administered at doses with relevant pharmacodynamic effects (≥0.3 g/kg) to healthy subjects who were classified as moderate drinkers. The studies used different routes of ethanol administration (oral, intravenous, and intraduodenal) with or without prior intake of food and after eating a meal during the time course of the study. Blood sampling schedules were appropriate to cover the absorption, distribution, and elimination phases of ethanol metabolism. A summary of the different study designs and demographic characteristics of the subjects included in each study is shown in Table 1.

In contrast to the studies performed by Jones22 and Hahn et al,23 numerical data were no longer available for the study performed by Ammon et al24. GetData Graph Digitizer 2.26 (http://getdata-graph-digitizer.com/) was used to extract observed BAC profiles from graphs in the original publication. Extracted molar concentrations for unlabeled (d0) and deuterium (d3)-labeled ethanol were both converted to g/L d0-ethanol to ensure comparability between the data sets. Information on administered ethanol doses, BW, and sex were also taken directly from the original publication.

Pooling the data resulted in a combined data set of 1510 ethanol concentrations (432 capillary and 1078 venous samples) from 72 healthy subjects (60 men, 12 women) between 20 and 60 years after oral, intraduodenal, and intravenous administration of ethanol in the fed and fasted state.

Population PK Analysis

Software. NONMEM 7.5.0 (ICON plc, Dublin, Ireland), Perl speaks NONMEM (PsN 5.2.6), Pirana 2.9.9 (Certara, Princeton, New Jersey), and R version 4.0.3 (https://www.r-project.org/) were used for data analysis and presentation. The first-order conditional estimation method with interaction was used throughout model building.

Pharmacokinetic Model Development. Separate population PK models were built for each study, followed by a joint analysis of the combined data set. Structural 1-, 2-, and 3-compartment models with first-order, zero-order, and Michaelis-Menten elimination kinetics were evaluated. To describe the absorption process, first-, zero-, and parallel zero-
### Table 1: Study Designs and Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Jones</th>
<th>Hahn et al</th>
<th>Ammon et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects (male/female)</td>
<td>48 (48/0)</td>
<td>12 (6/6)</td>
<td>12 (6/6)</td>
</tr>
<tr>
<td>No. of samples</td>
<td>432</td>
<td>456</td>
<td>622</td>
</tr>
<tr>
<td>Route of administration</td>
<td>PO</td>
<td>IV</td>
<td>First occasion: IV + PO/ID Second occasion: IV + ID/PO</td>
</tr>
<tr>
<td>Ethanol dose</td>
<td>0.68 g/kg in equally divided portions within 20 minutes</td>
<td>$2 \times 0.4$ g/kg over 45 minutes</td>
<td>$0.3$ g/kg $d_0$- and $0.3$ g/kg $d_3$-ethanol concomitantly on each occasion $^a$</td>
</tr>
<tr>
<td>Food intake during the study</td>
<td>Administration in the fasted state; a meal was served after 5 h</td>
<td>Subjects received 2 infusions of the same dose on the same day, of which 1 was preceded by a meal</td>
<td>Administration on both occasions in the fed state 30 min after intake of a standardized lunch</td>
</tr>
<tr>
<td>Sample type</td>
<td>Capillary blood</td>
<td>Venous blood</td>
<td>Venous blood</td>
</tr>
<tr>
<td>Ethanol quantification (LLOQ)</td>
<td>Automated enzymatic method using ADH and NAD$^+$ (NA)</td>
<td>Headspace gas chromatography (NA)</td>
<td>Gas chromatography/mass spectrometry (0.0023 g/L)</td>
</tr>
<tr>
<td>Sampling times after start of administration</td>
<td>0.5, 1, 1.5, 2, 3, 4.5, 6, and 7 h</td>
<td>0 (before dosing), 5, 10, 15, 30, 45, 50, 55, 60, 65, 70, 75, 80, and 90 min, and at 1.75, 2, 2.25, 2.75, 3, 3.67, 4 h</td>
<td>0 (before dosing), 10, 20, 30, 45, 60, 75, and 90 min, and at 2, 2.5, 3, 4, 5, 6 h</td>
</tr>
<tr>
<td>Demographic characteristics$^a$</td>
<td>Age (y) 39 (20-60)</td>
<td>36 (21-50)</td>
<td>NA (24-52)</td>
</tr>
<tr>
<td></td>
<td>Weight (kg) 80.25 (61-100)</td>
<td>75.95 (59-97)</td>
<td>68 (47-87)</td>
</tr>
<tr>
<td></td>
<td>Height (cm) 182 (170-191)</td>
<td>172 (157-194)</td>
<td>NA</td>
</tr>
</tbody>
</table>

ADH, alcohol dehydrogenase; LLOQ, lower limit of quantification; NA, not available; NAD$^+$, nicotinamide adenine dinucleotide.

$^a$ Demographic characteristics are given as median (range).

$^b$ On both occasions, all subjects received an intravenous infusion of unlabeled ($d_0$)-ethanol. Concomitantly, an equimolar dose of deuterium ($d_3$)-labeled ethanol was administered either orally (PO) or intraduodenally (ID).

First-order absorption models with and without lag times or additional transit compartments were explored. Ethanol bioavailability was estimated if intestinal administration data was modeled together with intravenous administration and was otherwise assumed to be 100%. Different approaches were tested to model capillary and venous ethanol concentrations simultaneously in the combined analysis (Figure S1). Separate absorption rates were estimated for oral ethanol administration in the fed and fasted states. The influence of food intake on ethanol elimination was incorporated into the models using a factor changing the elimination rate of ethanol in the fed state. Time-dependent linear or exponential changes in this food effect (FE) on ethanol elimination were investigated.

PK parameters were assumed to follow a log-normal distribution. Interindividual variability was tested on all PK parameters using an exponential model. Shrinkage $<30\%$ was considered acceptable.  Interoccasion variability was explored in the study performed by Ammon et al$^{24}$ using an additional exponential random-effects term. Additive, proportional, and combined (additive and proportional) error models were evaluated to describe the residual unexplained variability.

Model selection was performed according to standard criteria based on the objective function value (OFV) and the Akaike information criterion for nested and nonnested models, respectively; goodness-of-fit plots; nonparametric bootstrap analyses ($n = 1000$)$^{26}$; and prediction-corrected visual predictive checks ($n = 1000$)$^{27}$.

Covariate Analysis. If available for the respective study and the combined data set, the effect of sex, age, BW, TBW,$^{28}$ and BMI on PK parameters of ethanol was evaluated. No information on individual age, height, TBW, and BMI was available for the study performed by Ammon et al$^{24}$.

Continuous covariates were normalized by the respective median value and modeled using a power model. A proportional model was used for categorical covariates. First, all covariates were added separately to the respective base model to establish a ranking of significant ($\Delta$OFV $\geq$ 3.84; $P < .05$) covariates. Respective covariates were then added sequentially in the ranking order to the base model and were retained in the model if the addition caused a significant model improvement. The various descriptors of body mass...
(BW, TBW, and BMI) were not added simultaneously on the same PK parameter, and only the one with the largest improvement of the model was considered. Any covariate was finally retained in the final model if the removal caused an increase in the OFV of at least 10.8 points (backward elimination; \( P < .001 \)).

**Model-Based Simulations**

BAC profiles were predicted based on population estimates of the combined model for a typical subject weighing 75 kg after receiving an ethanol dose of 45 g (0.6 g/kg) to illustrate the effect of different absorption rate constant (\( K_a \)) values (scenario 1), food intake (scenario 2), oral administration schemes (scenario 3), and intravenous infusion times (scenario 4) on the AUC from time 0 to 10 hours (AUC\(_{0-10h}\)) and \( C_{\text{max}} \). Venous sampling was assumed in all scenarios. AUCs were determined by simulation using NONMEM 7.5.0.

In scenario 1, oral ethanol administration over 20 minutes was simulated in the fasted state. Besides the population estimate for \( K_a \) in the fasted state obtained from the combined model, 2 \( K_a \) values (\( K_a = 1 \) and 8 per hour) were taken from the literature to cover a range of reported values in the fasted state.\(^27,29\)

Scenario 2 assumed oral ethanol administration over 20 minutes in the fasted state, either without food intake during the entire profile or with food intake after 2 and 4 hours, respectively. In scenario 3, ethanol was administered orally in the fed state either as a bolus dose, over 20 minutes’ drinking time, or in 7 equally divided portions within 1 hour. Intravenous administration of ethanol in the fasted state with infusion times of 10, 30, and 60 minutes was simulated in scenario 4.

**Results**

**Population PK Analysis**

**Individual Studies.** BAC profiles were best described by a 2-compartment model (1, central; 2, peripheral) with first-order absorption and saturable Michaelis-Menten elimination kinetics in all 3 studies. In the study performed by Ammon et al.\(^{24}\), concentrations of \( d_0 \)- and \( d_3 \)-ethanol were modeled simultaneously in separate compartments. PK parameters were set to be equal for \( d_0 \)- and \( d_3 \)-ethanol, and mutual competitive inhibition of \( d_0 \)- and \( d_1 \)-ethanol was assumed for the elimination process (Figure S7). The Michaelis-Menten constant (\( K_m \)) could not be estimated in the study performed by Hahn et al.\(^ {23}\) and was fixed to 0.0821 g/L according to the literature.\(^{31}\) In the studies performed by Jones\(^ {22}\) and Hahn et al.\(^ {23}\) \( V_{\text{max}} \) was defined as:

\[
V_{\text{maxfed}} = \theta V_{\text{max, fasted}} \times \theta FE
\]

The implementation of an FE describing a change in \( V_{\text{max}} \) after intake of food considerably improved both models (\( \Delta \text{OFV Jones} = -169.6 \), \( \Delta \text{OFV Hahn et al.} = -372.6 \)).

Population estimates for \( V_{\text{max, fasted}} \) and the FE were 6.24 g/h (95% CI, 5.87-6.63 g/h) and 1.45-fold (95% CI, 1.37-1.53-fold) in the study performed by Jones.\(^{22}\) and 6.84 g/h (95% CI, 6.25-7.44 g/h) and 1.36-fold (95% CI, 1.26-1.48-fold) in the study performed by Hahn et al.\(^ {23}\) \( V_{\text{max}} \) was estimated to be 8.3 g/h (95% CI, 7.85-8.72) in the study performed by Ammon et al.\(^ {24}\) where all samples were collected in the fed state.

Adding a linear time decrease in the FE significantly improved the model in the study performed by Hahn et al.\(^ {23}\) The time decrease was estimated to be 0.093-fold per hour (\( \Delta \text{OFV} = 5.8 \)). However, the model got unstable after the implementation and the estimate was obtained with a relative standard error >60%. The linear time decrease was therefore not included into the final model. No significant OFV improvements were observed when a linear or exponential time decrease in the FE was implemented in the studies performed by Jones\(^ {22}\) or Ammon et al.\(^ {24}\)

Ethanol bioavailability could be estimated in the study performed by Ammon et al.\(^ {24}\) and was 95.3% (95% CI, 92.7-97.7) and 98.4% (95% CI, 95.3-100) after oral and intraduodenal administration, respectively. All results of the separated population PK analyses are shown in Table 2. Detailed results of the covariate analyses for the individual studies are provided in Table 3.

The following covariates were retained in the final models after stepwise covariate model building: TBW on the volume of distribution in the peripheral compartment \( (V_{\text{per}}) \) in the study performed by Jones.\(^ {22}\) TBW on the volume of distribution in the central compartment \( (V_{\text{cen}}) \) and BW on \( V_{\text{per}} \) in the study performed by Hahn et al.\(^ {23}\) and sex and BW on \( V_{\text{per}} \) in the study performed by Ammon et al.\(^ {24}\)

**Combined Analysis.** All dynamic approaches to fit capillary and venous BAC simultaneously were not supported by the data. An overview of the tested models with a description of why they failed is shown in Figure S1. Therefore, separate values for \( V_{\text{d}} \), the intercompartmental clearance, and \( K_m \) were estimated for capillary and venous BAC. This allowed a joint estimation of \( V_{\text{max}} \) and the FE, and a combined covariate analysis could be performed. Capillary and venous BAC profiles were both described by a 2-compartment model (1, central; 2, peripheral). The model structure of the joint analysis is shown in Figure 1. \( V_{\text{max}} \) was defined as:

\[
V_{\text{maxfed}} = \theta V_{\text{max, fasted}} \times \theta FE
\]

The implementation of an FE improved the OFV by 600 points. \( V_{\text{max, fasted}} \) and the FE were estimated...
to be 6.31 g/h (95% CI, 6.04-6.59 g/h) and 1.39-fold (95% CI, 1.33-1.46-fold), respectively. Neither a linear or exponential decrease nor an increase in the FE over time significantly improved the combined model.

Ethanol bioavailability was estimated to be 94.4% (95% CI, 91.8-97.2) and 98.2% (95% CI, 95.1-100.0) after oral and intraduodenal administration, respectively. Separate estimates were obtained to describe the residual unexplained variability for each study. All results of the joint population pharmacokinetic analysis are shown in Table 4.

Information on sex and BW were available for all subjects in the combined data set and were therefore tested as covariates on PK parameters of ethanol (Table 3). After stepwise covariate model building, BW on Vper was the only covariate retained in the combined model.

**Model Evaluation**

Standard goodness-of-fit plots indicated that the combined model (Figure 2) and the individual models (Figure S8) were able to describe observed BAC profiles reasonably without significant trends. Prediction-corrected visual predictive checks showed that the final models adequately described both the central tendency and spread of the observed data (Figures 3 and S9). However, a slight underprediction for low BACs following oral administration was visible in the combined model (Figure 3).

Plots depicting observed BAC profiles for every individual together with individual model predictions also

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate [RSE%] (Shrinkage)</th>
<th>Bootstrap Median [95%CI]</th>
<th>Estimate [RSE%] (Shrinkage)</th>
<th>Bootstrap Median [95%CI]</th>
<th>Estimate [RSE%] (Shrinkage)</th>
<th>Bootstrap Median [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Km (g/L)</td>
<td>0.0142 [4]</td>
<td>0.0145</td>
<td>0.0821 [5]</td>
<td>0.0853 [9]</td>
<td>0.0084</td>
<td></td>
</tr>
<tr>
<td>Kquadrinal (per hour)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10.4 [10]</td>
<td>10.2 [6.45-18.8]</td>
</tr>
<tr>
<td>Q (L/h)</td>
<td>44.8 [10]</td>
<td>44.3 [35.0-52.9]</td>
<td>95.7 [12]</td>
<td>94.6 [73.7-116.7]</td>
<td>120 [5]</td>
<td>118.5 [100.2-148.0]</td>
</tr>
<tr>
<td>Foral</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.953 [1]</td>
<td>0.951 [0.927-0.977]</td>
</tr>
<tr>
<td>Fduodenal</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.39 [9]</td>
<td>1.39 [1.16-1.65]</td>
</tr>
<tr>
<td>TBW Vmax (power)</td>
<td>–</td>
<td>–</td>
<td>1.84 [24]</td>
<td>1.91 [0.8-3.0]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TBW Vper (power)</td>
<td>3.38 [9]</td>
<td>3.4 [2.76-4.26]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BW Vper (power)</td>
<td>–</td>
<td>–</td>
<td>1.26 [10]</td>
<td>1.25 [0.6-1.7]</td>
<td>0.86 [17]</td>
<td>0.86 [0.56-1.2]</td>
</tr>
<tr>
<td>Sex Vper</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.24 [25]</td>
<td>0.24 [0.14-0.36]</td>
</tr>
<tr>
<td>Interindividual variability (CV%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koral</td>
<td>101.9 [10] (6)</td>
<td>101.4 [78.6-133.4]</td>
<td>–</td>
<td>–</td>
<td>27.2 [18] (0)</td>
<td>25.5 [15.4-34.8]</td>
</tr>
<tr>
<td>Food effect Vmax</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5.4 [19] (24)</td>
<td>5.2 [3.1-7.3]</td>
</tr>
<tr>
<td>IOV Vmax (CV%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.953 [1]</td>
<td>0.951 [0.927-0.977]</td>
</tr>
<tr>
<td>Residual variability (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive error</td>
<td>0.019 [6]</td>
<td>0.019 [0.016-0.021]</td>
<td>0.0356 [6]</td>
<td>0.0356</td>
<td>0.0037 [25]</td>
<td>0.0036</td>
</tr>
<tr>
<td>Proportional error</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.109 [6]</td>
<td>0.109 [0.094-0.116]</td>
</tr>
</tbody>
</table>

BW, body weight; CI, confidence interval; CV%, coefficient of variation in percent calculated as $100 \times \sqrt{\exp(\omega^2) - 1}$; $F_{\text{duodenal}}$, bioavailability following intraduodenal administration; $F_{\text{oral}}$, bioavailability following oral administration; IOV, interoccasion variability; $K_{\text{oral}}$, absorbance rate constant following oral administration; $K_{\text{quadrinal}}$, absorption rate constant following intraduodenal administration; $K_{\text{oral}}$, Michaelis-Menten constant; PK, pharmacokinetic; Q, intercompartmental clearance; RSE%, relative standard error in percent; SD, standard deviation; TBW, total body water; Vcen, volume of distribution in the central compartment; $V_{\text{max}}$, maximum elimination rate of ethanol; Vper, volume of distribution in the peripheral compartment.

a Jones and Hahn et al: estimate obtained in the fasted state ($V_{\text{max,fasted}}$), Ammon et al: estimate obtained in the fed state ($V_{\text{max,fed}}$).

b Jones and Hahn et al: $V_{\text{max,fed}}$ = $V_{\text{max,fasted}} \times$ Food effect.

c Ammon et al $V_{\text{per}} = 27.7 \times (\text{BW}/68)^{0.86} \times (1 + \text{sex} \times 0.24)$, where sex = 0 if female and sex = 1 if male.
Table 3. Results of the Covariate Analysis

<table>
<thead>
<tr>
<th>∆OFV Compared to Base</th>
<th>Jones</th>
<th>Hahn et al</th>
<th>Ammon et al</th>
<th>Combined Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model Without Covariates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food effect on $V_{max}$</td>
<td>$-169.6$</td>
<td>$-372.6$</td>
<td>NA</td>
<td>$-599.5$</td>
</tr>
<tr>
<td>Sex on $K_{a,d}$oral</td>
<td>NA</td>
<td>NA</td>
<td>$-0.029$</td>
<td>$-0.059^b$</td>
</tr>
<tr>
<td>Sex on $K_{a,oral}$</td>
<td>NA</td>
<td>NA</td>
<td>$-0.007$</td>
<td>$-0.192$</td>
</tr>
<tr>
<td>Age on $K_{a,d}$oral</td>
<td>$-0.447$</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age on $V_{max}$</td>
<td>$-0.72$</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sex on $V_{max}$</td>
<td>NA</td>
<td>$-3.6$</td>
<td>$-4.6$</td>
<td>$-1.7$</td>
</tr>
<tr>
<td>BW on $V_{cen}$</td>
<td>$-22.8$</td>
<td>$-5.7$</td>
<td>$-2.1$</td>
<td>$-27.4$</td>
</tr>
<tr>
<td>TBW on $V_{cen}$</td>
<td>$-27.7$</td>
<td>$-10.3$</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BMI on $V_{cen}$</td>
<td>$-15.2$</td>
<td>$-0.05$</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sex on $V_{cen}$</td>
<td>NA</td>
<td>$0.34$</td>
<td>$0.01$</td>
<td>NA</td>
</tr>
<tr>
<td>BW on $V_{per}$</td>
<td>$-49.9$</td>
<td>$-93.3$</td>
<td>$-13.7$</td>
<td>$-56.4$</td>
</tr>
<tr>
<td>TBW on $V_{per}$</td>
<td>$-57.4$</td>
<td>$-78.8$</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BMI on $V_{per}$</td>
<td>$-21.7$</td>
<td>$-9.5$</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age on $V_{per}$</td>
<td>$-3.25$</td>
<td>$0.37$</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sex on $V_{per}$</td>
<td>NA</td>
<td>$-33.2$</td>
<td>$-10.9$</td>
<td>$-9.7$</td>
</tr>
</tbody>
</table>

BMI, body mass index; BW, body weight; $K_{a,oral}$, absorption rate constant following oral administration; $K_{a,d}$oral, absorption rate constant following intraduodenal administration; $V_{cen}$, volume of distribution in the central compartment; $V_{max}$, maximum elimination rate; $V_{per}$, volume of distribution in the peripheral compartment.

Decrease in the OFV of at least 3.84 points was considered significant ($P < .05$).

$V_{max,fast} = V_{max,fasted} \times$ Food effect.

Could be tested only on $K_{a,oral,fast}$.

---

demonstrated good fit (Figures S2-S6 and S10-S14). Median parameter estimates and 95% CIs obtained from bootstrap analyses for the individual models and the combined analysis are shown in Tables 2 and 4, respectively. Shrinkage did not exceed 29% in any of the models.

Model-Based Simulations

Figure 4 shows simulated BAC curves with obtained AUC$_{0-10h}$ and $C_{max}$ values for scenarios 1-4. A lower $K_{a,oral}$ and slower intravenous infusion rates were related to reduced AUC$_{0-10h}$ and $C_{max}$ values (scenarios 1 and 4). AUC$_{0-10h}$ reductions of 17% and 8% were observed when food was ingested 2 or 4 hours after the start of oral ethanol administration as compared to a simulated curve with no food intake (scenario 2).

Similar AUC$_{0-10h}$ and $C_{max}$ values were obtained when ethanol was administered either orally as a bolus dose or over 20 minutes’ drinking time in the fed state, while the fractionated administration of 7 single doses over 1 hour resulted in lower AUC$_{0-10h}$ and $C_{max}$ values (scenario 3).

Discussion

The present population PK analysis of published BAC profiles showed that the effect of food on the PK of oral ethanol is mainly caused by the effect on ethanol elimination and less so by the effect on absorption rate, and that first-pass metabolism of ethanol was essentially negligible at the doses used. Simulations illustrated that AUC does not reflect bioavailability when elimination is saturated.

Previously, structural 1-, 30,32–34 2-,35–37 and 3-compartment38,39 models with first-order absorption and Michaelis-Menten elimination kinetics were used to describe the PK of ethanol. In our analysis, BAC profiles from 3 published clinical studies were best described by 2-compartment models with first-order absorption and Michaelis-Menten elimination kinetics.

Population estimates for $V_{cen}$ and $V_{per}$ differed significantly between the individual studies. Taking into account differences in median BW (Table 1), the combined consideration of individual estimates for $V_{cen}$ and $V_{per}$ leads to more uniform results for the average $V_d$: 0.72 L/kg for men (Jones22), 0.62 L/kg for men and 0.49 L/kg for women (Hahn et al23), and 0.59 L/kg for men and 0.5 L/kg for women (Ammon et al24). These results are in accordance with reports in the literature.3,6

Population estimates for $K_m$ differed considerably between the studies performed by Jones22 (0.0142 g/L) and Ammon et al24 (0.0853 g/L). This deviation was also evident in the combined model, where $K_m$ was estimated to be 0.0121 g/L and 0.0849 g/L for capillary and venous BAC, respectively. However, estimates for $K_m$ in our analyses are consistent with results from previous studies and reflect the wide range of reported $K_m$ values (0.01-1.3 g/L) in the literature.3,31,34 This may be attributable to both the small number of data...
Figure 1. Model structure of the combined model. Separate estimates for the volumes of distribution ($V_{\text{central}}$, $V_{\text{peripheral}}$), the intercompartmental clearance ($Q$), and the Michaelis-Menten constant ($K_m$) were obtained for capillary and venous ethanol concentrations, respectively. Capillary estimate was obtained for capillary ethanol concentrations; $d_0$-ethanol, unlabeled ethanol; $d_3$-ethanol, deuterium ($d_3$)-labeled ethanol; $K_a$, absorption rate constant; $V_{\text{max}}$, maximum elimination rate of ethanol; venous, estimate was obtained for venous ethanol concentrations.

points with low ethanol concentrations and to the fact that many individual enzymes (including different heterodimers of ADHs) with different $K_m$ values contribute to ethanol metabolism, which cannot be separated by empirical estimation of $K_m$ values from in vivo data.

The intake of food together with ethanol delays gastric emptying and prolongs ethanol absorption.\(^6\),\(^7\),\(^8\) Consistently, food intake tripled the observed absorption half-time of ethanol with estimated $K_{a,\text{oral}}$ values of 1.38 per hour in the fed state (Ammon et al\(^24\)) and 3.79 per hour in the fasted state (Jones\(^22\)). Similar values were obtained in the combined analysis. \(^6\),\(^7\),\(^8\) $K_{a,\text{oral}}$ in the fed state was reported to be 4.4 per hour and 4.6 per hour in 2 studies.\(^22\),\(^23\) $K_{a,\text{oral}}$ values observed in the fasted state range from 1 to 8 per hour.\(^29\),\(^30\),\(^33\),\(^38\) Considering the observed variability concerning this parameter, our estimates for $K_{a,\text{oral}}$ are in line with results from the literature. Population estimates for $K_{a,\text{duodenal}}$ were up to 8-fold higher than the values obtained for $K_{a,\text{oral}}$. The rate of ethanol absorption does not depend on gastric emptying when ethanol is administered directly into the duodenum, in which the majority of ingested ethanol is absorbed.\(^6\)

This leads to a considerably accelerated absorption process.

Obtained values for $V_{\text{max, fed}}$ were similar in the 3 individual studies (Jones\(^22\): $V_{\text{max, fed}}$ of 6.24 g/h $\times$ 1.45 = $V_{\text{max, fed}}$ of 9.05 g/h; Hahn et al\(^23\): $V_{\text{max, fed}}$ of 6.84 g/h $\times$ 1.36 = $V_{\text{max, fed}}$ of 9.3 g/h; Ammon et al\(^24\): $V_{\text{max, fed}}$ of 8.3 g/h). These results are consistent with those of the combined analysis: $V_{\text{max, fed}}$ of 6.31 g/h $\times$ 1.39 = $V_{\text{max, fed}}$ of 8.77 g/h. Our finding that food intake increases the elimination rate of ethanol by about 40% is in line with reported results in the literature.\(^19\),\(^21\)

Several studies have shown that the elimination rate of ethanol from blood is increased after eating a meal and also when nutrients were administered intravenously, compared to the fasting state.\(^19\),\(^21\),\(^23\),\(^40\),\(^41\) These effects were independent of any effect of food intake on the rate of ethanol absorption from the gut. However, the underlying mechanisms remain unclear. It appears that meals rich in amino acids are more efficient in boosting rate of ethanol clearance from blood compared with other dietary components, such as carbohydrates.\(^20\)

Ramchandani et al\(^21\) found that elimination rates of ethanol were increased regardless of the meal...
Figure 2. Goodness-of-fit (GOF) plots for the combined analysis stratified by administration site. (a) Intravenous administration, (b) oral administration, and (c) intraduodenal administration. Black lines represent lines of identity or lines of 0 residuals. Red lines indicate locally weighted smoothing lines. CWRES, conditional weighted residuals.

Figure 3. Prediction-corrected visual predictive checks (n = 1000) for the combined analysis stratified by administration site. (a) Intravenous administration, (b) oral administration, and (c) intraduodenal administration. Solid lines represent the median (red) and the 10th and 90th percentiles (black) of prediction-corrected observations. Shaded areas indicate the 95% confidence intervals around the median (red) and the 10th and 90th percentiles (blue) of prediction-corrected simulated data.
Table 4. Parameter Estimates of the Combined Model (Bootstrap n = 1000)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>RSE% (Shrinkage)</th>
<th>Bootstrap Median [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vmax (g/h)(^a)</td>
<td>6.31</td>
<td>2</td>
<td>6.3 [6.04-6.59]</td>
</tr>
<tr>
<td>Km,venous (g/L)</td>
<td>0.0849</td>
<td>10</td>
<td>0.0842 [0.069-0.105]</td>
</tr>
<tr>
<td>Km,capillary (g/L)</td>
<td>0.0121</td>
<td>25</td>
<td>0.0115 [0.0037-0.022]</td>
</tr>
<tr>
<td>Ka,oral,fed (per hour)</td>
<td>1.45</td>
<td>10</td>
<td>1.44 [1.2-1.77]</td>
</tr>
<tr>
<td>Ka,oral,fasted (per hour)</td>
<td>3.64</td>
<td>12</td>
<td>3.67 [2.9-5.48]</td>
</tr>
<tr>
<td>Ka,duodenal (per hour)</td>
<td>11.2</td>
<td>16</td>
<td>11.4 [9.9-21.0]</td>
</tr>
<tr>
<td>Vcen,venous (L)</td>
<td>11.1</td>
<td>13</td>
<td>11.1 [8.1-13.6]</td>
</tr>
<tr>
<td>Vcen,capillary (L)</td>
<td>32.6</td>
<td>5</td>
<td>32.7 [30.2-36.0]</td>
</tr>
<tr>
<td>Qvenous (L/h)</td>
<td>96.8</td>
<td>7</td>
<td>96.8 [84.5-110.3]</td>
</tr>
<tr>
<td>Qcapillary (L/h)</td>
<td>47.7</td>
<td>10</td>
<td>47.0 [37.2-56.5]</td>
</tr>
<tr>
<td>Vper,venous (L)</td>
<td>24.4</td>
<td>6</td>
<td>24.2 [21.1-27.0]</td>
</tr>
<tr>
<td>Food effect Vmax</td>
<td>0.944</td>
<td>1</td>
<td>0.944 [0.918-0.972]</td>
</tr>
<tr>
<td>BW Vper (power)</td>
<td>1.49</td>
<td>9</td>
<td>1.5 [1.1-1.88]</td>
</tr>
<tr>
<td><strong>Interindividual variability (CV%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vmax</td>
<td>13.5</td>
<td>11 (7)</td>
<td>13.3 [10.5-16.4]</td>
</tr>
<tr>
<td>Km,oral,fed</td>
<td>31.9</td>
<td>14 (0)</td>
<td>29.8 [19.9-38.7]</td>
</tr>
<tr>
<td>Km,oral,fasted</td>
<td>97.1</td>
<td>9 (5)</td>
<td>97.1 [74.0-125.5]</td>
</tr>
<tr>
<td>Ka,duodenal</td>
<td>105.8</td>
<td>23 (6)</td>
<td>95.1 [45.8-247.9]</td>
</tr>
<tr>
<td>Vcen,venous</td>
<td>57.9</td>
<td>23 (6)</td>
<td>56.1 [33.9-107.3]</td>
</tr>
<tr>
<td>Qvenous</td>
<td>26.4</td>
<td>28 (20)</td>
<td>25.3 [7.7-40.0]</td>
</tr>
<tr>
<td>Qcapillary</td>
<td>38.5</td>
<td>15 (14)</td>
<td>38.0 [26.2-48.5]</td>
</tr>
<tr>
<td>Vper,venous</td>
<td>17.1</td>
<td>16 (7)</td>
<td>16.5 [11.5-22.7]</td>
</tr>
<tr>
<td>Vper,capillary</td>
<td>14.1</td>
<td>14 (7)</td>
<td>13.7 [10.4-18.3]</td>
</tr>
<tr>
<td>Food effect Vmax</td>
<td>10.6</td>
<td>17 (29)</td>
<td>10.3 [5.9-13.7]</td>
</tr>
<tr>
<td>IOV Vmax (CV%)</td>
<td>5.5</td>
<td>19 (27)</td>
<td>5.2 [3.2-7.5]</td>
</tr>
<tr>
<td><strong>Residual variability (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive error, Jones</td>
<td>0.018</td>
<td>7</td>
<td>0.018 [0.0154-0.02]</td>
</tr>
<tr>
<td>Additive error, Hahn et al</td>
<td>0.036</td>
<td>6</td>
<td>0.035 [0.031-0.039]</td>
</tr>
<tr>
<td>Additive error, Ammon et al</td>
<td>0.102</td>
<td>6</td>
<td>0.1 [0.086-0.113]</td>
</tr>
<tr>
<td>Proportional error, Ammon et al</td>
<td>0.0038</td>
<td></td>
<td>0.0038 [0.0026-0.0069]</td>
</tr>
</tbody>
</table>

BW, body weight; CI, confidence interval; CV%, coefficient of variation in percent calculated as \(100 \times \sqrt{\exp(\omega^2)} - 1\); F\textsubscript{duodenal}, bioavailability following intraduodenal administration; F\textsubscript{oral}, bioavailability following oral administration; IOV, interoccasion variability; K\textsubscript{ch,duodenal}, absorption rate constant following intraduodenal administration; K\textsubscript{ch,oral}, absorption rate constant following oral administration; Km, Michaelis-Menten constant; Q, intercompartmental clearance; RSE%, relative standard error in percent; SD, standard deviation; Vmax, maximum elimination rate of ethanol; Vcen, volume of distribution in the central compartment; Vper, volume of distribution in the peripheral compartment.

Venous, estimate obtained for venous measurements (Hahn et al and Ammon et al); capillary, estimate obtained for capillary measurements (Jones).

\(^a\)Estimate obtained for the fasted state, \(V_{\text{max, fed}} = V_{\text{max, fasted}} \times \text{Food effect}\).

\(^b\)Estimate obtained for the study performed by Ammon et al.

composition, with high-carbohydrate, high-protein, or high-fat meals being equally effective. The authors mention that previous studies\(^{42}\) indicated an increased liver blood flow after food intake.

After intravenous administration of ethanol, the rate of elimination from blood showed a statistically significant increase after treatment with amino acids as compared to equicaloric glucose or Ringer’s acetate.\(^{20}\) The authors suggested that this finding might be explained by an increased hepatic mitochondrial respiratory activity after treatment with amino acids and hence a more effective reoxidation of NADH to NAD\(^+\) (reduced and oxidized forms, respectively, of nicotinamide adenine dinucleotide).\(^{43}\) The reoxidation of NADH to NAD\(^+\) has previously been proposed as the rate-limiting step in the hepatic oxidation of ethanol.\(^{44}\) In this case, a more effective regeneration of NAD\(^+\) would result in an increased ethanol elimination rate.\(^{20}\) In another study, high-carbohydrate meals caused a significant increase in the elimination rate of ethanol as compared to the fasted state, while no significant effect was observed for high-protein or high-fat meals.\(^{40}\) It could also be shown that both glucose and fructose accelerate ethanol metabolism, whereas potential mechanisms remain controversial.\(^{45-47}\) A recent study indicates that the effect of fructose on ethanol elimination is mediated by an increased NADH consumption of hepatocytes after fructose administration.\(^{48}\) In the present analysis,
the composition of administered meals is known only for the study performed by Ammon et al., where all subjects received chicken with rice (27 g fat, 5 g protein, 57 g carbohydrates, 381 kcal) 30 minutes before ethanol administration. Lower peak BAC and smaller AUCs are observed when ethanol is consumed together with food. Food affects the PK of ethanol in 2 ways: It slows down ethanol absorption by delayed gastric emptying, and it increases the elimination rate of ethanol. In case of saturable elimination, the AUC is not linear to the administered dose and/or the input rate. Accordingly, lower $K_a$ values or prolonged intravenous infusion rates reduce observed BAC and lead to lower AUCs (Figure 4), irrespective of any first-pass metabolism. The combined effect of food intake on ethanol absorption and elimination is difficult to illustrate given the large variability of reported $K_a$ values in the

Figure 4. Simulations for a typical subject (75 kg, ethanol dose: 0.6 g/kg) based on the population estimates of the combined model. (a) Scenario 1: oral administration with different absorption rate constants ($K_a$). (b) Scenario 2: oral administration in the fasted state ($K_a = 3.64$ per hour) with either no food or food intake at 2 and 4 hours after start of administration. (c) Scenario 3: oral administration in the fed state ($K_a = 1.45$ per hour) as a bolus dose, over 20 minutes, and divided into 7 fractions over 1 hour. (d) Scenario 4: intravenous administration over 10, 30, and 60 minutes in the fasted state. AUC$_{0-10h}$ area under the concentration-time curve from time 0 to 10 hours.
metabolism after food intake when gastric emptying is
affect initial BACs. It is systemically available, while these scenarios would
in the stomach in the case of delayed emptying, or
dose is kept outside the body and drunk later, stored
elimination of a given dose in terms of grams per hour,
that first-pass metabolism may reduce BACs. For the
from the intestine directly to the liver or the gastric mu-
At saturation conditions, providing additional ethanol
and pronounced induction of low-affinity CYP2E1.
least in individuals without a history of heavy drinking
ethanol absorption in the fed state contributed to a
Based on mechanistic considerations, unless very
low doses are used, in most situations it is not rea-
ton any relevant first-pass metabolism of ethanol.8 Upon oral ethanol intake in the social
drinking range, ethanol is rapidly absorbed and dis-
tributed in the entire body and results in BACs at
which the major eliminating enzymes are saturated, at
least in individuals without a history of heavy drinking
and pronounced induction of low-affinity CYP2E1. At saturation conditions, providing additional ethanol
from the intestine directly to the liver or the gastric mu-
cosa cannot increase ethanol turnover, which excludes
that first-pass metabolism may reduce BACs. For the
elimination of a given dose in terms of grams per hour,
at saturation it should not matter whether part of the
dose is kept outside the body and drunk later, stored
in the stomach in the case of delayed emptying, or
is systemically available, while these scenarios would
affect initial BACs.

The extent to which ethanol undergoes first-pass
metabolism is reported to depend on the ingested dose
and the rate of absorption, with increased first-pass
metabolism after food intake when gastric emptying is slow.6,6 These reports, however, need to be scrutinized
because the nonlinear relationship between AUC and
dose/rate of absorption in case of saturable elimination
(see above) precludes a valid assessment of bioavail-
ability and hence first-pass metabolism based on AUC
comparisons.7,49–51

Ammon et al24 were aware of this problem and
addressed it by different ethanol administration rates
to account for the effect of different absorption rates
but still used AUC to assess bioavailability. Our analysis
especially confirms their results of the noncompart-
mental analysis that ethanol bioavailability, even when
given in the fed state, is close to 100%.

In summary, our results along with mechanistic
PK considerations confirm that first-pass metabolism
of ethanol is essentially negligible, at least for doses
with relevant pharmacodynamic effects and for indi-
viduals without major CYP2E1 induction. Con-
tradictory results also relating to food effects may
mainly be based on delayed absorption and the in-
appropriate use of AUC values to estimate first-pass
metabolism.

The influence of BW could be tested as a covariate
on PK parameters of ethanol in all individual analyses
and in the combined data set. Except for Vcen in the
individual analysis of the study performed by Ammon et al.24 BW had a significant influence on Vcen and Vper
in all evaluations during forward inclusion (Table 3).

In addition to BW, TBW and BMI were included as
covariates on PK parameters of ethanol in the indi-
vidual analyses of the studies reported by Jones22 and
Hahn et al.23 Vcen and Vper were significantly affected by
TBW in both evaluations when it was added separately
to the respective base model. BMI had a significant
influence on Vcen and Vper in the study performed by
Jones, and a significant influence on Vper in the study
performed by Hahn et al.

After absorption into the bloodstream, ethanol does not bind to plasma proteins or other macro-
molecules and is rapidly distributed into the TBW
compartment.3,4 Accordingly, our evaluations show that,
based on the extent of OFV reduction and re-
tained covariates in the final models, TBW alone was
superior to BW alone in explaining interindividual
variability in Vcen and Vper in the studies performed
by Jones22 and Hahn et al.23 BW considered together
with sex was equivalent to TBW. Both TBW and BW
performed better than BMI.

The Vd of ethanol varies between men, women, and
age groups because of differences in body fat content
and a decrease in body fluid volumes with age.6 Besides
BW, sex was retained as a covariate on Vper in the final
model of the study performed by Ammon et al.24 No
significant effect of age on Vcen or Vper was observed
in the studies performed by Jones22 and Hahn et al.23
where this covariate could be tested. This might be
explained by the inclusion of relatively young subjects
in both studies, with the oldest volunteers being 60
(Jones) and 50 years old (Hahn et al). In contrast
to previous evaluations, we observed no significant
relationship between age and Vmax or Ka,oral.32

The present analysis has some limitations. All eval-
uated studies were conducted in White populations,
which limits the extrapolation of our results to other
populations. Crossover data including both oral and
intravenous ethanol administration was available only
for subjects in the study performed by Ammon et al24
(n = 12). Attempts to obtain further crossover data
from previously published studies were unsuccessful,
since primary data were no longer available.

The combined data set included both capillary and
venous BAC. It is well known that there are time-
dependent differences between capillary and venous
BAC that must be considered during the model-
building process.52 Dynamic approaches to cope with
these capillary-venous BAC differences were unsuccessful, but common estimates of $V_{\text{max}}$ in the fasted state and the FE could be obtained.

There were indications for a linear decrease in the FE over time in the study performed by Hahn et al. However, a reliable estimate for this decrease could not be obtained in the present analysis, and further studies are required to reveal time dependencies in the FE.

For the subjects included in the study reported by Ammon et al., only information on BW and sex was available. Thus, only BW and sex were evaluated as covariates in the individual analysis of the study performed by Ammon et al and in the combined data set. A comparison of the influence of body mass descriptors (BW, TBW, and BMI) on PK parameters of ethanol was possible only in the individual analyses of the studies reported by Jones and Hahn et al. In the studies performed by Jones and Hahn et al, regression equations incorporating sex, age, height, and BW were used to calculate TBW. However, the $V_d$ of ethanol ($V_{\text{cen}} + V_{\text{per}}$) can itself serve as an estimate of TBW if the database is of good quality. Another limitation was the unavailability of ADH and aldehyde dehydrogenase genotypes in all 3 studies, which therefore could not be tested as covariates on PK parameters of ethanol.

**Conclusion**

The PK model we present here has allowed us to differentiate the effects of food intake on the rate of absorption and metabolism of ethanol and to combine these into a single kinetic model. The lower AUC observed in the fed state was mainly accounted for by an increased rate of ethanol elimination from the bloodstream more so than by a decreased rate of ethanol absorption. Further studies are required to investigate the underlying mechanisms of the effect of food on the elimination rate of ethanol. First-pass metabolism of orally or intraduodenally administered ethanol was essentially negligible at the doses used in the evaluated studies. Because of the existence of saturation kinetics, the bioavailability of ethanol should not be determined by comparison of AUC after oral and intravenous administration.

Our PK model might be useful in clinical pharmacology when individual BAC predictions are made in relation to covariates, such as food intake, mode of administration, or body mass descriptors. The PK model we describe might also have applications in forensic and legal medicine, such as when alcohol-related crimes are investigated. Predicting a person’s BAC on the basis of a given consumption pattern and also back-extrapolating BAC at the time of sampling to an earlier time, are often required in forensic casework.

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**Author Contributions**

All authors contributed to the conception and design of the research. A.W.J., R.G.H., M.S., and U.K. provided the data. S.B. organized the database and performed the analyses. U.F. supervised the project. S.B. wrote the first draft of the manuscript. A.W.J., R.G.H., and U.F. wrote sections of the manuscript. All authors reviewed and approved the submitted version of the manuscript.

**Conflicts of Interest**

The authors declare no conflicts of interest.

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**Data Availability Statement**

The data that support the findings of this study are available on request from the corresponding author.

**Pharmacometric Studies**

The NONMEM control streams for the individual PK analyses and the combined analysis are provided in the Supplemental Information.

**References**


**Supplemental Information**

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.