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Population pharmacokinetics of multiple alcohol intake in humans

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ABSTRACT

The objective of this study was to determine population-based pharmacokinetics parameters for ethanol following multiple intake and to identify the factors influencing the pharmacokinetics. Three different solutions of alcoholic liquor (ethanol 55.39 ± 0.45 g) with different dissolved oxygen concentrations were administered, and blood alcohol concentration was determined in 59 healthy subjects using a breath analyzer. Samples ($n = 2955$) were collected at various time points. Population pharmacokinetic modeling was performed to describe the pharmacokinetics of ethanol. The influence of individuals' demography and dissolved oxygen concentration was investigated, and Visual Predictive Check and bootstrapping were conducted for internal evaluation. The developed model was used to perform simulations to visualize the effects of covariates on individuals. A one-compartment model with Michaelis–Menten elimination kinetics described the multiple ethanol intake data. Population pharmacokinetic estimates of V_{max} and K_m were 3.256 mmol min^{-1} and 0.8183 mmol L^{-1}, respectively. V_d/F was estimated to be 77.0 L, and K_a was 0.0767 min^{-1}. Body weight, age, and the dissolved oxygen concentration were confirmed to be significant covariates. The mean estimates from the developed population pharmacokinetic model were very similar to those from 500 bootstrap samples, and Visual Predictive Check showed that approximately 94% of the observed data fit well within the 5th–95th percentile. A one-compartment model with nonlinear elimination kinetics for multiple ethanol intake was developed and the significant covariates were determined. The robustness of the developed model was evaluated by bootstrap and Visual Predictive Check. The final model and implanted covariates explained well the variability and underlying mechanism of ethanol PK.

Introduction

Elimination of alcohol occurs mainly via hepatic oxidation and is governed by the three catalytic properties of the alcohol metabolizing enzymes including microsomal ethanol oxidizing system (MEOS) linked with cytochrome P-450, alcohol dehydrogenase (ADH) followed by aldehyde dehydrogenase (ALDH), and catalase (Baek, Lee, & Kwon, 2010; Norberg, Jones, Hahn, & Gabrielsson, 2003; Ramchandani, Bosron, & Li, 2001). The MEOS is known to be a contributor to the enzyme induction effect of metabolism and requires the NADPH and $NADP^+$ coenzymes along with an oxygen molecule to convert ethanol to acetaldehyde (Lieber, 1999; Lieber, Rubin, & DeCarli, 1970; Smith et al., 1993). The ADH pathway reversibly converts ethanol to acetaldehyde using NAD^+ and NADH (Umulis, Gürmen, Singh, & Fogler, 2005) (Fig. 1). Acetaldehyde is then irreversibly oxidized to acetate. The end products of this process are CO_2 and water, and oxygen (O_2) is assumed to contribute to metabolism via both pathways (Baek et al., 2010; Ramchandani et al., 2001; Umulis et al., 2005).

Gastro-enteric oxygen intake (via the stomach) is more intensive than breathing and supplies oxygen to both muscular cells and their regenerative processes. Also, the oxygen enriched water, applied into the stomach, affects the oxygenation of portal blood. Breathing increase the oxygen content of the liver by 8%, while oxygen absorbed through the stomach increases it by 43% (Forth & Adam, 2001).

Ethanol pharmacokinetics (PK) shows large inter- and intra-variability, and many studies over the past 70 years have attempted to explain this issue. One-, two-, and three-compartment models have thus far been proposed for ethanol PK (Fujimiya, Yamaoka, & Fukui, 1989; Mumenthaler, Taylor, & Yesavage, 2000; Rangno, Kreeft, & Sitar, 1981; Wedel, Pieters, Pikaar, & Ockhuizen, 1991). Zero-order elimination, nonlinear elimination, and parallel kinetics, which combines first-order

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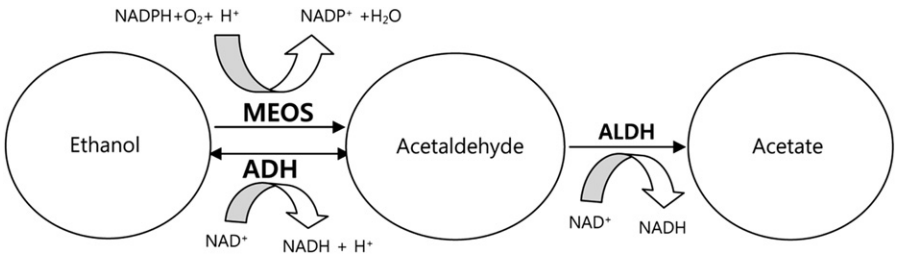

Fig. 1. The mechanism of ethanol metabolism. ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenase; MEOS = microsomal ethanol oxidizing system; NAD^+ = nicotinamide adenine dinucleotide; NADH = reduced form of NAD^+; $NADP^+$ = nicotinamide adenine dinucleotide phosphate; NADPH = reduced form of $NADP^+$.

elimination and nonlinear elimination, have been applied to ethanol elimination (Mumenthaler et al., 2000; Rangno et al., 1981; Winek & Murphy, 1984). In terms of the source of variability, factors such as gender, effect of food, body size, genetic polymorphism, and concentration of alcohol on ethanol PK have been investigated (Baraona et al., 2001; Bosron, Ehrig, & Li, 1997; Chen, Peng, Wang, Tsao, & Yin, 2009; Fraser, Rosalki, Gamble, & Pounder, 1995; Haddad et al., 1998; Higuchi, 1994; Kalant, 2000; Marshall, Kingstone, Boss, & Morgan, 1983; Norberg et al., 2003).

The oxygen-enriched spirit Soju, launched in 2007, contains 19.5% (v/v) ethanol and is the most popular alcoholic drink in Korea. The concentration of dissolved oxygen in this alcoholic beverage can be increased to 25 mg L^{-1} by the patented method of Sunyang Co., Ltd., Korea. Recently, there has been extensive publicity surrounding the suggestion that a high concentration of dissolved oxygen in alcohol may help reduce alcohol-related side effects. However, scientific evidence for this claim is still lacking. Therefore, we previously reported that the dissolved oxygen concentration also has an impact on the time to reach to 0.000% blood alcohol concentration (Baek et al., 2010). Most previous studies were based on a single intake of ethanol and the PK of repeated intake of alcoholic beverage remains to be documented. In previous studies, identifying the factors affecting PK and developing a PK model were conducted separately. The present study was designed to develop a PK model of multiple ethanol intake, which occurs in real-world situations. We here present a population PK model of ethanol in healthy adults, which we used to investigate the interrelationships of covariates (including dissolved oxygen concentration) with PK parameters using nonlinear mixed effects modeling (NONMEM). Estimation of both population and individual parameters was performed simultaneously.

Materials and methods

Experimental subjects

Two experiments were conducted based on a randomized, double-blind, and two-period crossover design (Baek et al., 2010). Thirty healthy volunteers per experiment were recruited, but one in the second experiment did not take part, so a total of 59 subjects participated in the pharmacokinetic evaluation; all were included in the analysis of blood alcohol concentration (BAC). Eleven of the 59 subjects participated in both the first and second experiments. All subjects passed the physical examination and laboratory screening. The study protocol was approved by the ethics committee of the Institute of Drug Research and Development at Chungnam National University (Daejeon, South Korea) with the Helsinki Declaration. These studies were conducted in conformance with informed consent. The demography of the study population is summarized in Table 1.

Study design

The design and BAC results from this study were described in detail by Baek et al. (2010). Briefly, in the first experiment, 360 mL of alcoholic beverage (Sunyang Co., Ltd., Daejeon, South Korea) with either 8 mg L^{-1} or 20 mg L^{-1} dissolved oxygen was assigned and administered in 40 min to 30 participants. The washout period between crossover experiments was 1 week. To mimic real-world situations and to avoid a diurnal effect, liquors were supplied after 17:00 h with standardized food containing 755 kcal (sautéed kimchi, a tangerine, tofu, and dried food). The subjects received a total of 55.35 ± 0.45 g ethanol with this food. To avoid vomiting and delaying gastric emptying, an aliquot (40 mL) was administered with food every 5 min. The BAC was determined by converting the breath alcohol concentration (BrAC) using a Lion Alcometer SD-400 (Lion Laboratories Ltd., Wales, UK). Instruments were validated using 0.100% alcohol standard gas according to the International Standard Organization (ISO9002:BS5750) protocol. Breath sampling points were changed on each occasion, depending on the previous BAC. A BrAC reading was taken every 30 min until the BAC reached 0.015%. Measurement intervals were 20 min at $0.01 < \text{BAC\%} \leq 0.015$ and 10 min at $\text{BAC\%} \leq 0.01$. When the BAC was less than 0.006%, samples were measured every 5 min until it reached 0.000%. Water (200 mL) was provided with food and then once per hour afterward. The second experiment was performed 2 months later with another 29 subjects using the same protocol; 11 of these were volunteers from the first study. The alcoholic beverage with 25 mg L^{-1} (instead of 20 mg L^{-1}) and 8 mg L^{-1} dissolved oxygen were supplied to the subjects in this second experiment.

Pharmacokinetic model

Modeling was performed using the first-order conditional estimation (FOCE) method in NONMEM ver. 6 (GloboMax LLC, Hanover,

Table 1
Basic characteristics of the study population (mean ± SD).

Characteristic	Mean ± SD
Gender (male/female)	39/20[a]
Age (years)	26.8 ± 4.5
Height (cm)	169.3 ± 8.1
Weight (kg)	61.3 ± 9.2
Red blood cell (M μL^{-1})	4.9 ± 0.4
Hemoglobin (g dL^{-1})	14.5 ± 1.5
Creatinine (mg dL^{-1})	0.9 ± 0.2
Total protein (g dL^{-1})	7.5 ± 0.3
Albumin (g dL^{-1})	4.7 ± 0.2
Total bilirubin (mg dL^{-1})	0.8 ± 0.3
Blood Urea Nitrogen (mg dL^{-1})	12.2 ± 2.7
Glucose (mg/dL)	87.9 ± 7.1
Total cholesterol (mg dL^{-1})	170.8 ± 30.7
Aspartate aminotransferase; AST (unit)	22.7 ± 7.2
Alanine aminotransferase; ALT (unit)	18.6 ± 10.0

[a] Eleven volunteers (nine males and one female) of 59 subjects participated in both the first and second experiments.