A Bayesian approach for population pharmacokinetic modeling of alcohol in Japanese Subjects

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INTRODUCTION & OBJECTIVES

- Genetic polymorphisms of aldehyde dehydrogenase 2 (ALDH2) gene has been known to affect alcohol metabolism. The blood alcohol concentrations (BACs) in subjects with the genetic variant *(ALDH2*2)* were known to be higher than subjects of homozygous wild-type (*ALDH2*1/*1*). However, **no PPK study for ethanol achieved success in identifying the genotype of *ALDH2* as a covariate**.
- Previously we conducted a PPK analysis of BACs for 34 Japanese healthy volunteers (Table 1, Study 1). The effect of *ALDH2* not being detected was probably attributable to **the poorly informative data from a relatively small number of subjects with a limited number of time points**.
- **Incorporation of external data to help stabilize the modeling process** has been suggested.[1]
- The **aim** of this study was to **explore significant covariates for the PPK analysis of alcohol** by incorporating **external data using a Bayesian method,** and estimate effects of the covariates.

METHODS

- A total of 157 BACs previously obtained from only the early part of the time-concentration curve in 34 Japanese subjects (**Table 1, Study 1**) were **re-analyzed with Markov chain Monte Carlo (MCMC) Bayesian analysis method in NONMEM 7.3.**
- **Priors for the population mean (PM) PK parameters** and for **the inter-individual variance of the PK parameters** are listed in **Table 2**. These were obtained from the parameter estimates of the final model (one-compartment model, with Michaelis-Menten elimination) reported by Seng *et al.* (**Table 1, Study 2**).
- **Inclusion criteria for each of the covariates** in the modeling process are
  1. **a decrease in the deviance**,
  2. **a decrease in the between subject variance** and/or **a decrease in the residual error** and
  3. **a clinically significant influence** on the parameter values, defined as **a change in the PM-PK parameter of at least 20% between subjects with the lowest and the highest covariate value** in the data set.

RESULTS

- The typical value for $\boldsymbol{V_d/F}$ was estimated to be 49.3L in subjects with *ALDH2*1/*1* (wild-type) and was **20.4 L (28%) smaller in subjects with *ALDH2*1/*2* (genetic variant)** (Table 3).
- The area under the time-BAC curve (AUC) for the subjects with *ALDH2*1/*2* was calculated 1.34 times higher than the subjects with *ALDH2*1/*1*.
- Age was shown to be positively correlated with $\boldsymbol{k_a}$ and shown to be negatively correlated with $\boldsymbol{V_d/F}$.

Table 1. Study [a] designs

Study No.	Population	n	Dose	Sampling plan	Basic PK model	Ref.
1	Japanese	13F, 21M	14 g of ethanol (350 mL of beer), 10 min in the fasted	5, 10, 20, 30, 60 min postdose	One-compartment	2
2	Chinese	36F, 31M	36 [b] and 56 [c] g of ethanol (200 [b] mL and 300 [c] mL of a	1.5, 2, 2.5, 3, 3.25, 3.5, 3.75, 4, 4.25,	One-compartment,	3
	Indian	43F, 44M	mixture of vodka and orange juice), 1 hr with a meal	4.5, 4.75, 5, 6 hr postdose	MM elimination	

[a] ref. 2 is a study the current dataset for re-analysis was obtained; ref. 3 is a study from which the prior information were obtained.
[b] a dose for female. [c] a dose for male. F, female; M, male; MM, Michaelis-Menten.

Table 2. Model building:
Effect of addition of covariates to the Base model

Model number and added covariates	Relationship(s) *	Posterior mean Deviance	σ^2
0: Base model	-	-1360	0.034
1: age on k_a	$k_a = \theta\times(age/29.4)^{\theta_{AGE(k_a)}}$	-1401	0.034
2: 1 plus age on V_d/F	$k_a = \theta\times(age/29.4)^{\theta_{AGE(k_a)}}$ $V_d/F = \theta\times(age/29.4)^{\theta_{AGE(V_d/F)}}$	-1401	0.034
3: 1 plus ALDH2 on V_d/F	$k_a = \theta\times(age/29.4)^{\theta_{age(k_a)}}$ $V_d/F = (\theta + \theta_{ALDH2(V_d/F)}\times ALDH2)$	-1412	0.031
4: 1 plus ALDH2 on k_a	$k_a = (\theta + \theta_{ALDH2(k_a)}\times ALDH2)\times(age/29.4)^{\theta_{AGE(k_a)}}$	-1401	0.034
5: 3 plus age on V_d/F	$k_a = \theta\times(age/29.4)^{\theta_{AGE(k_a)}}$ $V_d/F = (\theta + \theta_{ALDH2(V_d/F)}\times ALDH2)\times(age/29.4)^{\theta_{AGE(V_d/F)}}$	-1424	0.028
6: 5 plus ALDH2 on k_a	$k_a = (\theta + \theta_{ALDH2(k_a)}\times ALDH2)\times(age/29.4)^{\theta_{AGE(k_a)}}$ $V_d/F = (\theta + \theta_{ALDH2(V_d/F)}\times ALDH2)\times(age/29.4)^{\theta_{AGE(V_d/F)}}$	-1436	0.027

* The only different relationships compared to the Base model are presented.
θ, typical value of parameter in the base model
ALDH2 = 1 if *ALDH2* genotype is **1/*2*; ALDH2 = 0 if *ALDH2* genotype is **1/*1*.

Structural model for PK parameters and covariates in **the Base model**:

$$k_{a_i} = (k_a + \theta_{SEX(ka)} \times FEMALE) \times exp\left(\eta_{k_{a_i}}\right)$$
$$V_d/F_i = (V_d/F + \theta_{SEX(V_d/F)} \times FEMALE) \times (WT/61.3)^{\theta_{WT(V_d/F)}} \times exp\left(\eta_{V_d/F_i}\right)$$
$$V_{max_i} = V_{max_{ADH1B*2/*2}} \times (WT/61.3)^{\theta_{WT(V_{max})}} \times exp\left(\eta_{V_{max_i}}\right)^{\dagger}$$
$$K_{m_i} = K_m \times exp\left(\eta_{K_{m_i}}\right)$$

† $V_{max_{ADH2*2/*2}}$ is replaced with $V_{max_{ADH2*1/*2}}$ for the subject with $ADH2 * 1/* 2$.

Table 3. Parameter estimates of the Base model and the Final model, and the prior distributions used in the alcohol PPK analysis.

	Mean (SD) of normal prior or Mode of Inverse Wishart prior [#]	Estimate for parameters (95% CI) Base model	Final model
Population mean pharmacokinetic parameters			
k_a (1 / hr)	4.4 (0.48)	3.3 (2.7, 4.1)	3.0 (2.4, 3.9)
V_d/F (L)	50.2 (1.0)	49.7 (47.8,51.7)	49.3 (47.4, 51.2)
$V_{max\ ADH1B*2/*1}$ (mg/hr)	7760 (255)	7827 (7327,8310)	7790 (7403, 8264)
$V_{max\ ADH1B*2/*2}$ (mg/hr)	8060 (300)	8197 (7660,8731)	7966 (7422, 8483)
K_m (mg/L)	16.2 (6.9)	0.09 (0.01, 0.47)	0.074 (0.001, 0.391)
Regression parameters for covariate model			
$\theta_{AGE(k_a)}$	0.01 (1000)	-	2.7 (2.1, 3.4)
$\theta_{AGE(V_d/F)}$	0.01 (1000)	-	0.52 (0.19, 0.83)
$\theta_{ALDH2(V_d/F)}$ (L)	0.01 (1000)	-	-20.4 (-27.7, -10.9)
$\theta_{WT(V_d/F)}$	0.78 (0.09)	0.80 (0.63, 0.98)	0.78 (0.60, 0.95)
$\theta_{WT(V_{max})}$	0.79 (0.06)	0.77 (0.66, 0.89)	0.78 (0.66, 0.90)
$\theta_{SEX(k_a)}$ (1 / hr)	-1.9 (0.5)	-1.9 (-2.6, -1.1)	-1.3 (-2.1, -0.56)
$\theta_{SEX(V_d/F)}$ (L)	-11.4 (1.5)	-11.7 (-14.5, -8.8)	-12.2 (-15.0, -9.41)
Between subject variance			
$\omega_{k_a}^2$	0.29	0.66 (0.45, 0.95)	0.37 (0.24, 0.55)
$\omega_{V_d/F}^2$	0.025	0.028 (0.017, 0.044)	0.029 (0.018, 0.048)
$\omega_{V_{max}}^2$	0.026	0.027 (0.017, 0.042)	0.027 (0.017, 0.042)
$\omega_{K_m}^2$	1.04	1.11 (0.69, 1.77)	1.13 (0.69, 1.83)
Residual error (%RSE)			
σ^2	-	0.034 (0.026,0.044)	0.028 (0.020,0.038)

[#] All of values for prior distribution of model parameters except $\theta_{AGE(k_a)}$, $\theta_{AGE(V_d/F)}$ and $\theta_{ALDH2(V_d/F)}$ were from Seng *et al.*[3]

Structural model for PK parameters and covariates in **the Final model** ‡:

$$k_{a_i} = (k_a + \theta_{SEX(ka)} \times FEMALE) \times (age/29.4)^{\theta_{AGE(k_a)}} \times exp\left(\eta_{k_{a_i}}\right)$$
$$V_d/F_i = (V_d/F + \theta_{SEX(V_d/F)} \times FEMALE + \theta_{ALDH2(V_d/F)} \times ALDH2) \times (WT/61.3)^{\theta_{WT(V_d/F)}} \times (age/29.4)^{\theta_{AGE(V_d/F)}} \times exp\left(\eta_{V_d/F_i}\right)$$

‡ Structural model for V_{max_i} and K_{m_i} is the same as those in the Base model.

CONCLUSION

A PPK model for alcohol was updated. A Bayesian approach allowed interpretation of significant covariates relationships, even if the current dataset is not informative about all parameters. This is **the first study** reporting an estimate of **the effect of the ALDH2 genotype** as a covariate in a PPK model.

GLOSSARY: PK, population pharmacokinetic; PPK, population PK; PM, population mean; BAC, blood alcohol concentration; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; MCMC, Markov chain Monte Carlo; WT, body weight; SE, standard error; %RSE, percent relative standard error of the estimate, equal to SE/parameter estimate x 100; NS, not supported; 95% CI, 95% Credible Interval; OFV, objective function values.
NOTATION: k_a, the first-order absorption rate constant; V_d/F, the apparent volume of distribution; V_{max}, the maximum metabolic rate; $V_{max\ ADH2*2/*1}$, V_{max} of subjects carrying *ADH2*2/*1*; $V_{max\ ADH2*2/*2}$, V_{max} of subjects carrying *ADH2*2/*2*; K_m, Michaelis-Menten constant; $\theta_{cov\,(PK\ parameter\ )}$, a covariate scale factor for cov when cov is a continuous variable or the change in the PK parameter value when cov is an indicator variable; FEMALE, an indicator variable for sex of 0 (male) or 1 (female); ALDH2, an indicator variable for ALDH2 genotype of 0 (*ALDH2*1/*1*) or 1 (*ALDH2*1/*2*); k_{a_i}, V_d/F_i, $V_{max\ i}$, or $K_{m\ i}$ is k_a, V_d/F, V_{max} or K_m of the ith individual; η_{k_a}, $\eta_{V_d/F}$, $\eta_{V_{max}}$ or η_{K_m} is an inter-individual random effect normally distributed with a mean of zero and variance of $\omega_{k_a}^2$, ω_{V_d/F^2}, $\omega_{V_{max}}^2$ or $\omega_{K_m}^2$.

References
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