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Relationship between plasma concentration of β-hydroxybutyrate, acetoacetate, lactate and pyruvate and alcohol after oral or intravenous administration of alcohol to normal human subjects: a population pharmacodynamics (PD) analysis

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ABSTRACT **AIM:** To investigate the relationship between plasma concentration of β-hydroxybutyrate, acetoacetate, lactate, pyruvate, β-hydroxybutyrate/acetoacetate (H/A ratio) and lactate/pyruvate (L/P ratio) and alcohol by population PD analysis after oral or intravenous administration of alcohol. **METHODS:** An oral dose of alcohol equivalent to 1.02 g·L^{-1} total body water was administered to 14 normal human subjects and an IV infusion (30 min) dose of alcohol equivalent to 0.83 g·L^{-1} total body water was administered to 8 normal subjects. Venous blood was sampled for determination of alcohol (BAC), β-hydroxybutyrate, acetoacetate, lactate and pyruvate for 380 min after oral administration and for 340 min after IV administration. **RESULTS:** After oral administration, the average of C_0 for BAC was 666 ±81 mg·L^{-1}, and it was significantly lower than 1 020 mg·L^{-1} ($P<0.001$). The slope β for eliminate-phase was 2.29 ± 0.50 mg·L^{-1}·min^{-1}. After IV administration, C_0 was 756 ± 109 mg·L^{-1}, and the slope β for eliminate-phase was 2.45 ±0.51 mg·L^{-1}·min^{-1}. The C_0 was not significantly different from the expected value of 830 mg·L^{-1}. After oral or IV administration, the relationship between BAC and β-hydroxybutyrate, acetoacetate, lactate and pyruvate concentration and H/A and L/P ratio were investigated by population physiologic indirect response model, and the parameters were presented. Meanwhile, the H/A did not reach maximum at the end of the elimination phase of the alcohol, and it suggested that the liver continue to accumulate NADH at zero-orden metabolism phase of alcohol. The plot of BAC versus the plasma concentration of lactate showed an apparent counter-clockwise hysteresis. **CONCLUSION:** In general, venous blood L/P ratio is not a suitable index for the real time reflection of liver redox status because of the time lag change in concentration of lactate after administration of ethanol. The parameters provided here can be useful for future researches on the effect of alcohol on liver redox status.

KEY WORDS pharmacokinetics; pharmacodynamics; population PD model; ethanol; β-hydroxybutyrate

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Alcohol (ethanol) elimination by liver cytoplasma ADHs leads to a more reduced redox state of the free cytosolic NADH-NAD$^+$ system and increased the NADH/NAD$^+$ ratio. This shift is associated with changes in the rates of gluconeogenesis, fat synthesis and steroid hormone metabolism[1,2]. The raised NADH concentration in the cytoplasm of liver increases the lactate/pyruvate (L/P) ratio because of the increased activity of lactate dehydrogenase[3], and this increase is reflected in the increased blood lactate/pyruvate ratio. The reducing equivalents produced in the cytosol are transported to mitochondria using the malate-aspartate shuttle and other shuttles[3,4]. This process increases the mitochondria NADH/NAD$^+$ ra-

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Chin J Clin Pharmacol Ther 2005 Jan; 10(1)

tio and subsequently increases the mitochondria and plasma β-hydroxybutyrate/acetoacetate (H/A) ratio by increasing the activity of β-hydroxybutyrate dehydrogenase.

Many groups have investigated the changes in the redox state in the presence of alcohol, and mostly *in vitro*. A number of studies also used blood L/P or H/A ratio as a index of hepatic redox status[5-10]. However, whether or not the blood ratios can accurately reflect the liver redox status have not been fully proved. And no study has ever focused on the relationship between blood alcohol concentration and blood L/P and H/A ratios, especially in humans. So it is necessary to study the relationships between blood alcohol and lactate, pyruvate, β-hydroxybutyrate, acetoacetate, H/A and L/P ratio to verify whether or not the blood ratios can be used as a real-time marker for liver redox status.

It is well known that alcohol distribution is limited to total body water and that alcohol elimination from the blood follows Michaelis-Menten kinetics[11,12]. In this study, an oral dose of alcohol equivalent to 1.02 $g \cdot L^{-1}$ total body water was administered to 14 normal human subjects and an IV infusion (30 min) dose of alcohol equivalent to 0.83 $g \cdot L^{-1}$ total body water was administered to 8 normal subjects. Blood was sampled for determination of alcohol, β-hydroxybutyrate, acetoacetate, lactate and pyruvate. The relationships between blood alcohol concentration (BAC) and the plasma β-hydroxybutyrate, acetoacetate, lactate, pyruvate, H/A and L/P ratio were examined 380 min after oral administration and 340 min after IV administration.

1 MATERIALS AND METHODS

1.1 Subjects Fourteen, healthy, non-alcoholic volunteers (aged 27.4±6.8 years, height 170.0±8.2 cm, weight 67.8±10.3 kg, 9 males, 5 females) participated in the oral study. Subjects did not consume any alcoholic beverages and medications for at least 3 days and 2 weeks, respectively. Subjects fasting from midnight arrived at the outpatient clinic at about 8:30 AM. Women were tested for pregnancy and undertook the urine drug screen. After about 30 min bed rest, 5 ml venous blood sample was taken through an intravenous catheter placed in the antecubital vein, and the catheter was kept patent by using a slow saline drip. The oral dose of alcohol equivalent to 1.02 $g \cdot L^{-1}$ total body water was administered to subjects based on the calculation published[13]. At about 9:30 AM, the alcohol mixed in orange juice (1∶3, *v*/*v*) was consumed within 20 min. 5 ml venous blood was taken at 20, 40, 60, 80, 100, 120, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360 and 380 min after administration. 1 ml venous blood was kept for blood alcohol determination. About 4 ml venous blood was immediately centrifuged and the plasma was frozen in dry ice, and it was kept for the determination of the H/A and L/P ratios. Plasma samples were stored at −80 °C until assayed and blood samples were kept refrigerated. 1 hour after the alcohol consuming, subjects were allowed to eat or drink non-caffeinated beverages at random time. Food/liquid was limited to 250 calories per hour, and food composition was chosen from a tray provided by nutrition services.

Eight healthy subjects participated in the IV study (aged 31.4±7.1 years, height 170.6±7.8 cm, weight 69.2±14.1, 5 males, 3 females). Among the eight subjects, six subjects also participated in the oral study, and the interval between two studies was at least one week. The dose of alcohol equivalent to 0.83 $g \cdot L^{-1}$ total body water[13] was formulated as a 7.5% solution in saline and infused (Gemini PC-1 infusion apparatus, Imed Co., San Diego, CA) over 30 min into one antecubital vein of subjects. Blood was sampled from the other antecubital vein as described above. Subjects remained in the supine position during the infusion. Blood was taken at 0, 10, 15, 20, 30, 32, 35, 40, 45, 60, 75, 90, 120, 150, 180, 210, 240, 255, 270, 285, 300, 320, 340 minutes for whole blood alcohol concentration assay. Larger blood samples at 0, 15, 30, 45, 60, 90, 120, 180, 240, 270, 300, 320 and 340 minutes were taken for plasma and processed as described in the oral study. Food and drink were provided as described above.

1.2 Methods BAC in heparinized tube was assayed by the Sigma (St. Louis, MO) diagnostic kit (multiple test vial. cat no. 332−30) and calibrated by the standard solution (800 $mg \cdot L^{-1}$) purchased from the same company. A calibration curve was linear with the concentrations as follows: 12.5, 25, 50, 100, 200, 400 and 800 $mg \cdot L^{-1}$ ($r^2 = 0.999$). The detection limit was between 5 and 10 $mg \cdot L^{-1}$. BAC was determined within one week after sampling. Plasma β-hydroxybutyrate and pyruvate were also assayed by Sigma kits according to the directions. 80 μl plasma was used for the determination of β-hydroxybutyrate. Plasma concentrations of acetoacetate were assayed according to the directions[14]. All samples from one subject were assayed together. All enzymatic assays were time controlled and performed by Beckman DU-65 spectrophotometer (Fullerton, CA). Plasma lactate was assayed by Analox micro-stat GM7 analyzer according to the instructions of the reagent kit (Analox Instruments

USA, Lunenburg, MA). The detection limits for the pyruvate, β-hydroxybutyrate, acetoacetate and lactate were 0.005, 0.005, 0.004 and 0.15 mmol·L^{-1}, respectively. The inter-day coefficients of variation for pyruvate, β-hydroxybutyrate, acetoacetate and lactate assay were 10%, 13%, 20% and 10%, respectively. The inter-day coefficient of variation for ethanol was less than 6%.

1.3 Data analysis The pseudo-zero-order elimination rate of alcohol was calculated from a single linear regression equation (the Widmark equation): $C_t = C_0 - bT$[15]. The parameter β was the slope of the pseudolinear elimination phase of the blood alcohol concentration-time curve. This and all subsequent equations were analyzed with Statistica 3.0 b by the computer.

The time when the pseudolinear elimination phase ends (t^*) was predicted for the average alcohol data by the following equation[16]:

$$t^* = -[(1-1/e)/V_{max}]C_0 + K_m/V_{max} \quad \text{Equation 1}$$

e is the base of natural logarithm, K_m and V_{max} are estimated by the Michaelis-Menten elimination kinetics on blood alcohol concentration in the post-absorption-distribution phase[12]:

$$t = -(C_t/V_{max}) + (K_m/V_{max}) * \ln(C_0/C_t) + C_0/V_{max} \quad \text{Equation 2}$$

1.4 Population PD analysis A physiologic indirect stimulation-K_{in} model was used to describe the relationship of BAC to Lactate, β-hydroxybutyrate, H/A and L/P ratios[17] in both oral and IV studies.

$$\frac{dR}{dt} = K_{in}\left(1 + \frac{E_{max}C}{EC_{50}+C}\right) - K_{out}R \quad \text{Equation 3}$$

K_{in} and K_{out} are the input and output constant controlling the response variable R, respectively. E_{max} is the maximum effect and EC_{50} is 50% stimulatory concentration. R is a response variable.

A physiologic indirect stimulation-K_{out} model[17] was applied to fit the relationship of BAC to pyruvate and acetoacetate in both studies.

$$\frac{dR}{dt} = K_{in} - K_{out}\left(1 + \frac{E_{max}C}{EC_{50}+C}\right)R \quad \text{Equation 4}$$

The actual BAC observed was applied to fit the population indirect response model. Population software NONMEM (Version 5.1) was used to fit the PD model. Comparison between individual time groups was analyzed with *t* test. $P < 0.05$ was considered as significant.

2 RESULTS

2.1 Oral alcohol study result The C_{max} for alcohol was between 20 and 80 minutes and peaking time for most (ten subjects) was between 40 and 60 minutes. Using the Widmark equation, the calculated average (SD) C_0 was 666±81 mg·L^{-1} (range 548—805 mg·L^{-1}). The average β value was 2.29±0.50 mg·L^{-1}·min^{-1} (range 1 420—3.29 mg·L^{-1}·min^{-1}).

The fitted K_m, V_{max} and C_0 by equation 2 for alcohol metabolism were 65.6±30 mg·L^{-1}, 3.84±1.79 mg·L^{-1}·min^{-1} and 768±149 mg·L^{-1} ($r = 0.993$) by using the alcohol concentration data, respectively. Thus the time (t^*) at which the pseudolinear elimination phase for the average alcohol concentration ends (first-order elimination begins) was 153±25.5 minutes. The average BAC at time t^* was 320±53 mg·L^{-1} (Fig 1).

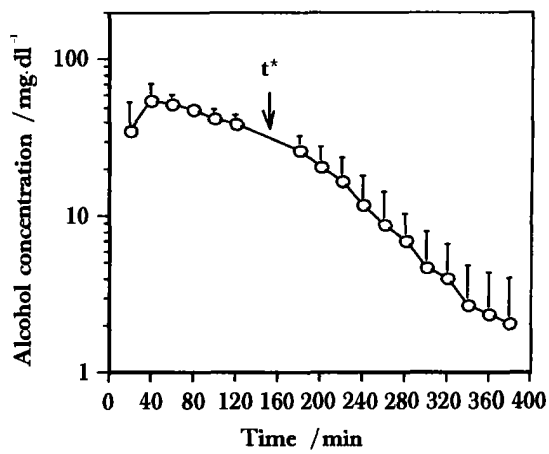

Fig 1 Log transformation of the average (SD) blood alcohol concentration (BAC) after oral dose of alcohol equivalent to 1.02 g·L^{-1} total body water administered to 14 human subjects.
t^*: The time that first-order elimination begins

The relationship of single compounds and blood alcohol was investigated by population indirect physiology model (Fig 2). Values of the PD parameters were shown in Tab 1. A slightly time-lagged increase was showed by lactate concentration, and the hysteresis curve was shown in Fig 2C. The average H/A ratio and L/P ratio were calculated as 2.3 and 21.1 at t^*, respectively. Assuming ethanol concentration can reach infinity, a maximum response (R_{max}) would be generated. Thus function 3 could be rearranged to $dR/dt = K_{in}(1 + S_{max}) - K_{out}R$, at R_{max}, $dR/dt = 0$, therefore, since $R_0 = K_{in}/K_{out}$, $R_{max} = (1 + S_{max}) \times R_0$. The maximum response ($R_{max}$) was calculated by the function as followed: $R_{max} = (1 + E_{max}) \times R_0$. Therefore, the average maximum H/A ratio and L/P ratio were 4.1 and 25.1, respectively. L/P ratio at t^* time showed 84% of maximum L/P ratio, and H/A ratio at t^* time showed only 56% of maximum H/A ratio. It indicated that L/P and H/A ratio were still increased at zero-order ethanol metabolism phase. The fitting curves from a representative individual were shown in Fig 3.

Chin J Clin Pharmacol Ther 2005 Jan; 10(1)

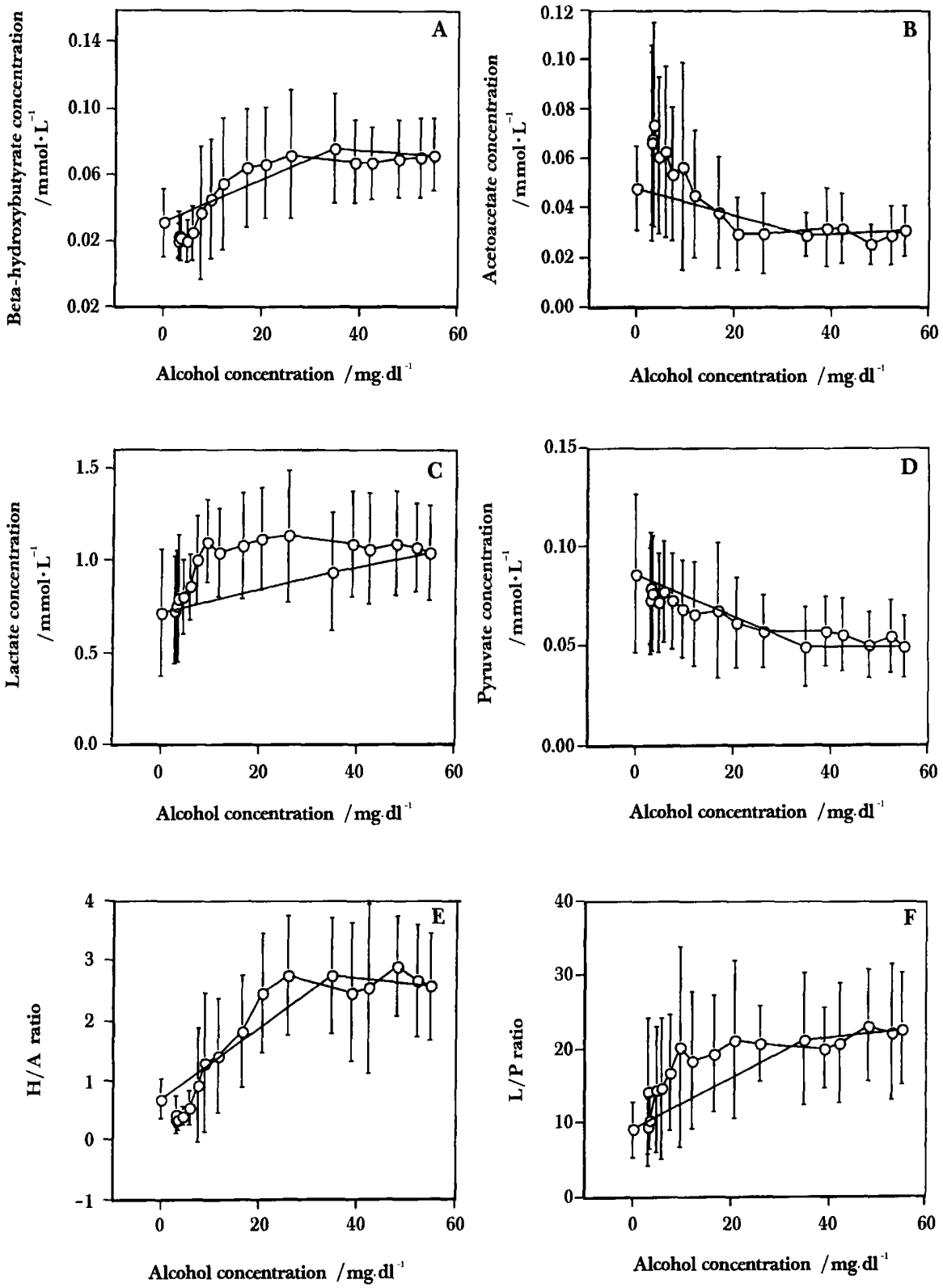

Fig 2 Plots of the single compounds versus blood alcohol concentration after oral dose of alcohol equivalent to 1.02 g·L^{-1} total body water administered to 14 human subjects

A: average plasma β-hydroxybutyrate concentration; B: average plasma acetoacetate concentration; C: average plasma lactate concentration; D: average plasma pyruvate concentration; E: average plasma H/A ratio; F: average plasma L/P ratio

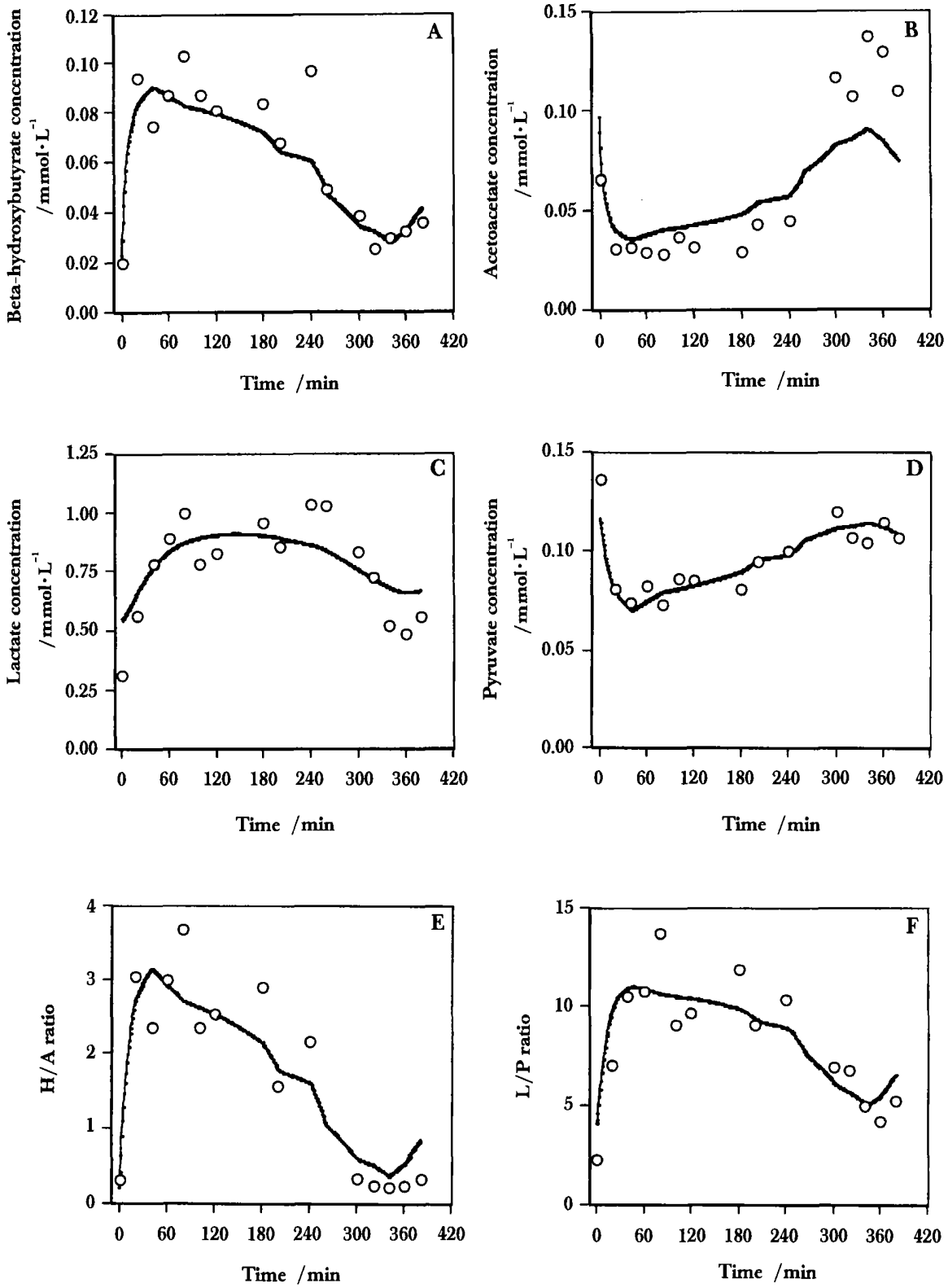

Fig 3　Plots of the single compounds versus blood alcohol concentration after oral dose of alcohol equivalent to 1.02 g·L^{-1} total body water administered to a individual subject. All curves were drawn by the population physiologic indirect response model.

A: β-hydroxybutyrate concentration; B: acetoacetate concentration; C: lactate concentration; D: pyruvate concentration; E: plasma H/A ratio; F: plasma L/P ratio

Tab 1　Parameters of β-hydroxybutyrate, acetoacetate, lactate, pyruvate, H/A ratio and L/P ratio data after oral and IV administration by using population method. Values in parenthes indicated the inter-subject variability (CV%)

	K_{in} /mmol·L^{-1}·min^{-1} *	E_{max}	EC_{50} /mg·dl^{-1}	K_{out} /min^{-1}
Oral beta-hydroxybutyrate	0.0282(13%)	3.63(59%)	15.9(267%)	1.5(—)
acetoacetate	0.084(35%)	3.95(—)	64.3(—)	1.17(—)
lactate	0.0259(30%)	0.789(—)	6(—)	0.0388(—)
pyruvate	0.0489(41%)	1.93(—)	143(55%)	0.663(—)
H/A ratio	0.205(—)	18.1(—)	27.6(—)	0.944(—)
L/P ratio	1.2(—)	2.09(35%)	10.1(113%)	0.147(—)
IVbeta-hydroxybutyrate	0.0238(31%)	3.01(—)	11.1(—)	0.95(—)
acetoacetate	0.0374(27%)	1.89(—)	39.3(—)	0.612(—)
lactate	0.00586(21%)	1.47(—)	12.6(—)	0.0112(—)
pyruvate	0.0256(51%)	2.35(54%)	127(—)	0.405(—)
H/A ratio	0.313(—)	10.2(—)	23.1(—)	0.812(—)
L/P ratio	0.65(—)	2.04(—)	7.49(—)	0.0756(—)

*: for ratio of H/A and L/P, the unit of K_{in} is min^{-1}

2.2　IV Alcohol study result　The C_0 calculated by Widmark equation was 756±109 mg·L^{-1} (range 645—912 mg·L^{-1}), and it is not significantly different than the expected value of 830 mg·L^{-1} (*t* test, $P>0.05$). The β was 2.45±0.51 mg·L^{-1}·min^{-1} and ranged 0.153—0.314. No significant difference was found between the oral and IV studies, and these values were also similar to those reported by others[18].

The fitted K_m, V_{max} and C_0 by equation 2 for alcohol metabolism were 29.7±17.7 mg·L^{-1}, 3.2±0.7 mg·L^{-1}·min^{-1} and 806±97 mg·L^{-1}, respectively by using alcohol concentration data. The values were similar to that reported by others[19]. Thus t^* was 169.9±26.8 min(Fig 4). The alcohol concentration at time t^* was 324±51 mg·L^{-1}, and it is almost identical to that of oral study.

Plots of the average BAC versus the average H/A ratio, L/P ratio, β-hydroxybutyrate (A), acetoacetate (B), lactate (C), and pyruvate (D) concentrations are presented in Fig 5. The fitted population PD parameters were shown in tab 1. The lactate concentrations at 15 min (0.64±0.18 mmol·L^{-1}) were significantly lower than that at 45 min (0.86±0.24 mmol·L^{-1}) or 60 min (0.80±0.21 mmol·L^{-1}) by paired *t*-test, and the ethanol concentrations at these time points were very similar ($P>0.05$, *t*-test). These results further confirmed the hysteresis in alcohol-lactate relationship. However, no hysteresis was observed for the relationships of other compounds and alcohol. The fitted curves for one representative individual (same subject as presented in Fig 3) were shown in Fig 6.

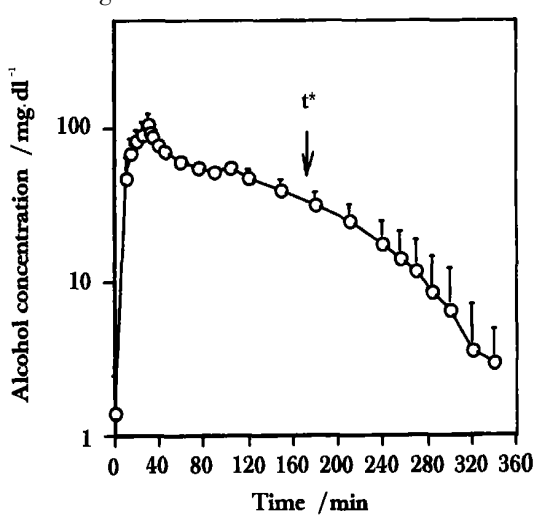

Fig 4　Log transformation of the average blood alcohol concentrations (BAC) after 30 minute intravenous infusion of alcohol equivalent to 0.83 g·L^{-1} total body water administered to 8 human subjects.

t^*: The time that first-order elimination begins

The average H/A ratio and L/P ratio were calculated as 2.7 and 22.9 at t^*, respectively. The maximum response (R_{max}) was calculated based on the function as followed: $R_{max}=(1+E_{max})*R_0$. Therefore, the average maximum H/A ratio and L/P ratio were 4.3 and 26.0, respectively. L/P ratio at t^* time was 88% of maximum L/P ratio, and H/A ratio at t^* time was only 63% of maximum H/A ratio. It indicated that L/P and H/A ratio did not reach maximum at t^* time in IV study.

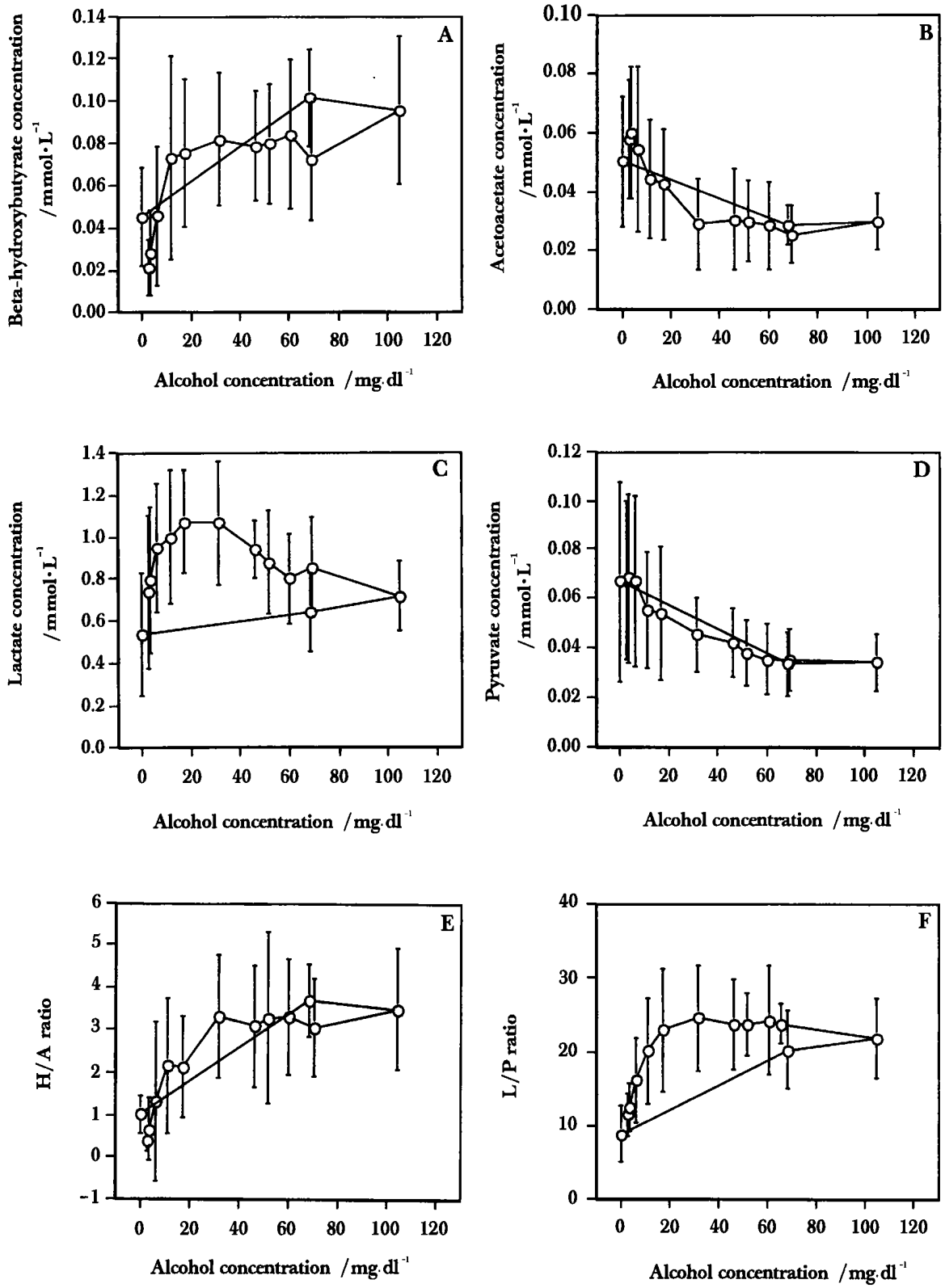

Fig 5　Plots of the single compounds versus blood alcohol concentration after 30 minute intravenous infusion of alcohol equivalent to 0.83 g·L^{-1} total body water administered to 8 human subjects

A: average plasma β-hydroxybutyrate concentration; B: average plasma acetoacetate concentration; C: average plasma lactate concentration; D: average plasma pyruvate concentration; E: average plasma H/A ratio; F: average plasma L/P ratio

Chin J Clin Pharmacol Ther 2005 Jan; 10(1)

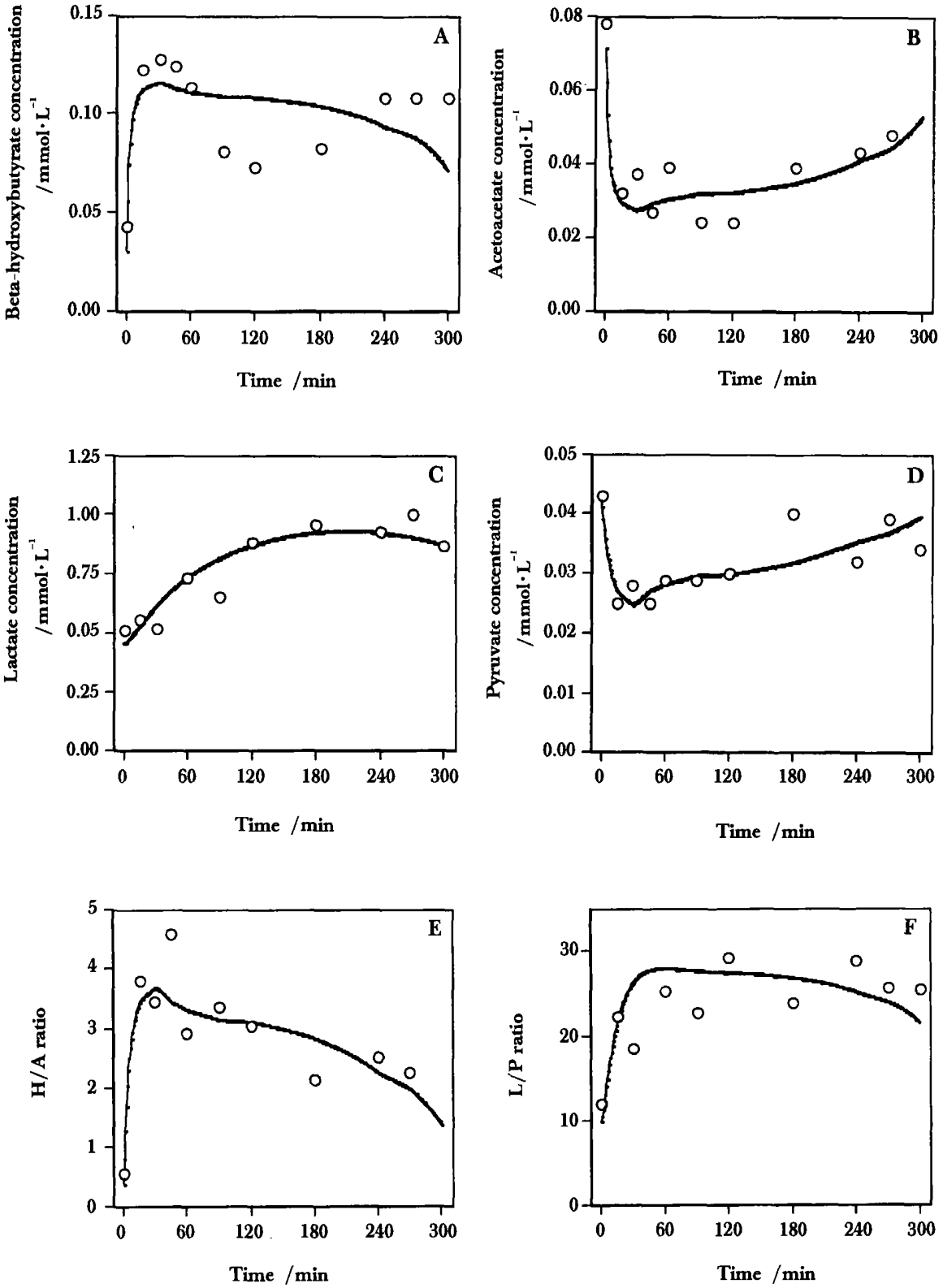

Fig 6 Plots of the single compounds versus blood alcohol concentration after intravenous infusion of alcohol equivalent to 0.83 g·L^{-1} total body water administered to a individual subject. All curves were drawn by the population physiologic indirect response model

A: β-hydroxybutyrate concentration; B: acetoacetate concentration; C: lactate concentration; D: pyruvate concentration; E: plasma H/A ratio; F: plasma L/P ratio

3 DISCUSSION

In the 30 minute infusion study, there was no significant difference between the measured C_0 and the expected value of 830 mg·L^{-1}. It suggested that the anthropomorphic calculation for total body water was valid.

In the oral study, the average C_0 calculated from both Widmark equation or equation 2 were significantly lower than 1 020 mg·L^{-1}, the value expected when the bioavailability of alcohol was 100%. In another oral study, the C_0 were lower than 800 mg·L^{-1} in both men and women when an alcohol dose of 1 141 mg·L^{-1} was adminited[20]. This result agrees with our study.

It is well known that alcohol undergoes first-pass metabolism before reaching the systemic circulation[21,22].

Although fasting can decrease the degree of first-pass metabolism[23], our data shows that the significant first-pass metabolism still exists and the prolonged absorption phase may be another explanation for the lowered C_0.

In both studies, the BAC versus H/A ratio, L/P ratio, β-hydroxybutyrate, acetoacetate, lactate and pyruvate were investigated with population PD indirect physiology model. To the best of our knowledge, no study has described such a relationship in either human or animal. The four compounds and H/A and L/P ratios for individual subjects usually fluctuated after intake of alcohol. Higher standard deviations in the ratios were also seen in other studies[5,8]. The fluctuations were not caused by assay or degradation of the compounds. It may be due to food intake as diet might affect the L/P ratio[6]. However, the effect of food on the H/A and L/P ratio seemed to be negligible compared with that by alcohol[5]. We carefully compared the time of food intake to the ratios and found that some fluctuations occurred before food intake. Also, the decreasing phases not seemed to be changed by food intake. Thus changes of ratio may largely reflect the unique effect of alcohol on the liver redox status.

Although no hysteresis was observed in plasma alcohol-H/A ratio relationship, we observed a counter-clock wise hysteresis loop in the alcohol-lactate relationship, over half of subjects in oral study showed apparent hysteresis in the alcohol-lactate relationship. This is probably due to delaying equilibration of lactate between the liver cytoplasm and the plasma due to the larger pool sizes of lactate, plasma lactate concentrations are more than 10-fold greater than pyruvate concentrations, and not a delay in alcohol when it reach the effect site, but there was no lag in changes in pyruvate concentration. The hysteresis in the alcohol-lactate relationship after IV administration was more apparent than that after oral administration. This difference is due to the more rapid increase in alcohol concentrations after IV administration. For alcohol can stimulate splanchnic releasing of lactate into blood[24], the BAC versus lactate concentration curve was fit by the physiologic indirect stimulation-K_{in} model developed by Jusko and Ko[17,25], which was able to solve the hysteresis when assuming the blood concentration of lactate was determined by a zero-order release rate constant from the organs and a first order uptake rate constant by the organs. As alcohol can stimulate splanchnic uptake of pyruvate from blood[24], the BAC versus pyruvate concentration curve was fit by physiologic indirect stimulation-K_{out} model[17]. Assuming the input of pyruvate into blood at a constant rate(K_{in}), alcohol was assumed to stimulate K_{out} with parameters of E_{max} and EC_{50}. There were many good agreements in K_{in} and K_{out} for pyruvate between oral and IV studies. As many organs such as muscle, heart, liver, etc can release and uptake lactate and pyruvate, the K_{in} and K_{out} just reflect a combined release and uptake rate to and from blood by those organs in normal condition. Regardless of the actual mechanisms that maintain blood lactate or pyruvate concentration, the increase or decrease of concentration in blood was driven predominantly by alcohol. EC_{50} is 50% of stimulatory concentration of alcohol. Our finding on the hysteresis in the alcohol-Lactate relationship indicates that it must be cautiously taken when L/P ratio was used as a real time reflection for liver redox status, although it is used in many studies[5-10]. Currently it is unclear that whether alcohol stimulate release or inhibit uptake of lactate and whether alcohol stimulate uptake or inhibit release of pyruvate in individual organ, therefore the models for relationship of alcohol vs lactate and pyruvate are based on our assumption mentioned above. However, we can use physiologic indirect stimulation-K_{in} model to fit the relationship of alcohol and the L/P ratio. As it is known that liver can deliver the ratio change to blood from cytoplasma in the presence of alcohol[3]. The disparities in some values between oral and IV studies probably due to the variability of the samples or some unknown reasons.

The BAC-β-hydroxybutyrate and BAC-acetoacetate relationships are also described by population PD model, although it is unclear that whether alcohol stimulate release or inhibit uptake of β-hydroxybutyrate and whether alcohol stimulate uptake or inhibit release of acetoacetate in each organ. We assume alcohol stimulate release of β-hydroxybutyrtt to blood from organs and stimalate uptake of acetoacetate from organs. The assumption described

above for lactate and pyruvate was made by the K_{in} and K_{out}. In general, the fitted parameters for BAC-β-hydroxybutyrate relationship and BAC-acetoacetate relationship between oral and IV studies are similar except two times difference in EC_{50} for β-hydroxybutyrate. This is probably due to deviation of the samples. As many organs such as kidney, muscle, heart, liver, etc can release and uptake β-hydroxybutyrate and acetoacetate, the K_{in} and K_{out} just reflect a combined release and uptake rate to and from blood by those organs in normal condition. Regardless of the actual mechanisms that maintain blood β-hydroxybutyrate or acetoacetate concentration, the increase or decrease of concentration in blood was stimulated predominantly by alcohol, and EC_{50} is 50% of the stimulatory concentration of alcohol. When the concentrations of alcohol approached zero, the acetoacetate concentrations were higher than zero time and β-hydroxybutyrate concentrations and H/A ratios were slightly lower than zero time although there was no statistical significance between these time points and zero time in some subjects. If it was true, the phenomena are probably caused by the rebound of activity of the β-hydroxybutyrate dehydrogenase, due to changes in mitochondrial homeostasis by ethanol. In general, these phenomena need to be further confirmed by larger sample size. The physiologic indirect stimulation-K_{in} model was used to analyze the relationship of alcohol and the H/A ratio. As it is known that liver can deliver the ratio change to blood from mitochondria in the presence of alcohol. Our study shows that H/A ratios was still increased at zero-order ethanol metabolism phase and that the NADH continue to accumulate, and that the producing capability of NADH exceed the removing capability of it at zero-order alcohol metabolism phase. This conclusion is also confirmed by L/P ratio which did not reach the maximum value at t^* time in both studies. The elevated NADH might function as a rate-limiting factor in alcohol metabolism. There is a opinion that a higher NADH concentration can inhibit ADH activity and play a important role as one of rate-limiting factors in ethanol metabolism[26]. On the other hand, it is suggested that there is no single rate-limiting step in the alcohol metabolism pathway and control is shared among several steps[27].

A physiologically-based compartmental pharmacodynamic model is not able to be established. Some parameters such as the pyruvate and acetoacetate clearance rate and lactate and β-hydroxybutyrate appearance rate, etc, in liver are not reported previously after literature search, and they are necessary to fit the model. Therefore we used a simple way-indirect physiology model to fit these relationships. The models assume that the drug (alcohol in our case) is the predominant driving force for blood substances change[17], considering the effect on the change from other factors minor or neglectable. This assumption is also employed in our case. Strictly, it follows "empirical" approach rather than mechanism based. Physiologic indirect response models are increasingly used by researchers in clinical pharmacology field due to its simplicity and capability to solve the hysteresis[28].

In general, it must be cautiously taken when using venous blood L/P ratio as a real time reflection for liver redox status because of the time-lagged change in lactate concentration after ethanol administration. The parameters provided here can be useful for future researches on the effect of alcohol on the four chemical compounds in blood and on liver redox status.

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口服及静注乙醇后血中乙醇与β-羟丁酸, 乙酰乙酸, 乳酸及丙酮酸浓度关系的探讨: 一项群体药效动力学的研究

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接要 目的: 应用群体药理学方法探讨血浆中乙醇浓度对β-羟 酸, 乙酰乙酸, 乳酸, 丙酮酸, β-羟 酸/乙酰乙酸(H/A)比值及乳酸/丙酮酸(L/P)比值变化的效应。方法: 给 14 名健康成人口服剂量相当于 1.02 g·L^{-1}总身体水的乙醇。在另一项实验中, 给 8 名健康成人静脉注射剂量相当于 0.83 g·L^{-1}总身体水的乙醇。在服用乙醇后 380 min 采取静脉血测定乙醇, β-羟 酸, 乙酰乙酸, 乳酸及丙酮酸的血浆浓度。在静注乙醇后 340 min 采血测定上述 5 种物质的血浆浓度。结果: 在口服乙醇实验中, C_0 为 66.6±8.1 mg·dl^{-1}, 显著低于 102 mg·dl^{-1}, (t 检验, $P<0.001$)。清除相斜率β为 0.229±0.05 mg·dl^{-1}·min^{-1}。在静注实验中, C_0 为 75.6±10.9 mg·dl^{-1}, 与 83 mg·dl^{-1} 比较无显著性差异, β为 0.245±0.05 mg·dl^{-1}·min^{-1}。在两项实验中, 我们应用群体间接生理反应模型来拟合乙醇浓度对β-羟 酸, 乙酰乙酸, 乳酸, 丙酮酸, β-羟 酸/乙酰乙酸比值及乳酸/丙酮酸比值变化的效应, 并得出各项参数。同时, 我们发现, 当乙醇的清除相结束时, H/A 比值尚未达最大值, 说明在乙醇的零级代谢相时肝脏仍在产生 NADH。乳酸和乙醇的关系曲线显示乳酸的变化呈现一种逆时钟方向的滞后。结论: 血 L/P 比值不适合用作实时肝脏氧化状态的指标。本研究提供的参数将有益于将来研究乙醇对肝脏氧化状态的影响。

关键词 药代动力学; 药效动力学; 群体药效学; 乙醇; β-羟 酸