Effect of high-fat, high-protein, and high-carbohydrate meals on the pharmacokinetics of a small dose of ethanol

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Aims To investigate whether the relative amounts of fat, carbohydrate (CHO), or protein in a meal influence the pharmacokinetics of a small dose of ethanol.

Methods Nine healthy men received ethanol ($0.30\ g\ kg^{-1}$ body weight) on five occasions in a randomized cross-over fashion. On three occasions the dose of ethanol was consumed within 15 min of eating a standardized breakfast of similar volume and calorific value but containing different amounts of fat, CHO, and protein. On two other occasions the same dose of ethanol was ingested on an empty stomach (overnight fast) or administered by intravenous (i.v.) infusion over 30 min.

Results The blood-ethanol profiles showed large inter and intraindividual variations, especially when ethanol was ingested after eating food. The peak blood-alcohol concentrations (BAC) were 16.6 ± 4.0, 17.7 ± 7.1, and $13.3 \pm 4.0\ mg\ dl^{-1}$ (mean $\pm$ s.d.) after fat, CHO, and protein-rich meals and 30.8 ± 4.3 and $54.3 \pm 6.4\ mg\ dl^{-1}$ after fasting and i.v. infusion, respectively. The corresponding areas under the concentration-time profiles (AUC) were 1767 ± 549, 1619 ± 760, $1270 \pm 406\ mg\ dl^{-1}$ min after fat, CHO, and protein-rich meals compared with 3210 ± 527 and $4786 \pm 446\ mg\ dl^{-1}$ min after fasting and i.v. infusion, respectively. The time required to eliminate ethanol from the blood was shortened by 1–2 h in the fed-state.

Conclusions Drinking ethanol after eating a meal, regardless of the nutritional composition, decreases the systemic availability of ethanol. Because gastric emptying is slow and more prolonged with food in the stomach, the delivery of ethanol to the duodenum and the liver will be highly variable as will the hepatic clearance of ethanol. Provided that portal venous BAC remains fairly low and ethanol metabolizing enzymes are not fully saturated then part of the dose of ethanol can be cleared by hepatic first-pass metabolism (FPM), as one consequence of Michaelis-Menten elimination kinetics.

Keywords: bioavailability, blood ethanol, first-pass metabolism, food, liver blood flow, macronutrients, pharmacokinetics

Introduction

Certain aspects of the pharmacokinetics of ethanol are important to consider in medicolegal casework when a person's BAC is estimated on the basis of a given drinking scenario [1–4]. These calculations almost always assume complete systemic availability of the dose of ethanol administered and negligible first-pass metabolism. However, this assumption may not be valid when small doses of ethanol are ingested with or after a meal [5–8].

Having food in the stomach before drinking delays gastric emptying. The rate of delivery of ethanol to the duodenum is slow and absorption of alcohol occurs predominantly through the stomach [9]. In the fed state, the peak BAC is considerably less and the entire BAC profile is reduced compared with drinking on an empty stomach [10, 11]. This means that the bioavailability of ethanol, as reflected in the area under the concentration-time curves (AUC) is diminished compared with parenteral (i.v. infusion) administration of the same dose [12, 13]. It seems that part of the dose of ethanol fails to reach the systemic circulation, presumably because of oxidation by alcohol dehydrogenase (ADH) enzymes located in the stomach and/or the liver [14, 15].

In the present study, we varied the proportions of fat, carbohydrate, and protein in a meal given to healthy volunteers prior to a small dose of ethanol ($0.30\ g\ kg^{-1}$). Accordingly, we established the concentration-time profiles of ethanol under fed conditions and also after an overnight fast. The same dose of ethanol was also given by intravenous (i.v.) infusion.

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Methods

Subjects and conditions

Nine healthy men, all nonsmokers, with a mean age of 24.6 years (s.d. = 4.8), body weight 75.8 kg (s.d. 9.0) and height

183 cm (s.d. 4.6) participated in this study as paid volunteers. The study protocol was approved by the local Ethics Committee and each subject took part in five experimental sessions with at least 7 days between treatments, although the intervals of time were not the same for all subjects. The dose of ethanol (0.30 g kg^{-1} body weight) was administered according to a randomized cross-over design either after the subjects had eaten a standardized breakfast or after an overnight fast or by intravenous infusion. The ethanol (96% v/v) was diluted with orange juice to give a 20% v/v cocktail and this was finished within exactly 15 min. The ethanol solution for i.v. infusion was prepared by the hospital pharmacy as a 6% w/v solution in saline and was administered at a constant rate over 30 min with the help of an IVAC model 560 infusion pump (San Diego, CA).

Meals were prepared from commonly available foodstuffs normally eaten for breakfast in Sweden and the individual components were chosen to contain relatively high proportions of fat (55% of total energy), protein (31%) or carbohydrate (86%), providing ≈3000 kJ (700 kcal) of energy. All meals were eaten in 15 min and the alcoholic drink was consumed a few minutes later. On two other occasions, the same dose of ethanol (0.30 g kg^{-1}) was ingested after an overnight (10 h) fast or was administered by constant rate intravenous infusion over 30 min.

Sampling of blood and determination of ethanol

Specimens of venous blood were obtained through an indwelling catheter predose and at exactly timed intervals of 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, and sometimes to 300 min from the start of alcohol dosing. The blood was taken into 5 ml Vacutainer tubes (Becton Dickinson Ltd, USA) containing NaF (40 mg) and heparin (143 units) as preservatives. The catheter tubing was flushed with a few drops of heparin-saline solution to prevent the blood from coagulating between the times of taking the samples.

The concentration of ethanol in blood was determined by headspace gas chromatography as described in detail elsewhere [16]. Aliquots of whole blood (100 μl) were removed from Vacutainer tubes and diluted 11-fold with *n*-propanol (8 mg dl^{-1}) as an internal standard. The blood and internal standard were ejected into headspace sampling vials (22 ml) which were immediately made air-tight with rubber stoppers and crimped-on aluminium caps. For gas chromatography, we used a glass column (2 m × 3 mm i.d.) packed with Carbopack C (0.2% Carbowax 1500 on Carbopack 80–100 mesh) as the stationary phase. The analytical precision expressed as the standard deviation (s.d.) of a single determination increases with the concentration of ethanol in the samples. At a mean BAC of 100 mg dl^{-1}, the s.d. was 0.8 mg dl^{-1} corresponding to a coefficient of variation of less than 1% [17]. The within-run s.d. for a single determination of ethanol at the limit of detection was 0.1 mg dl^{-1} which corresponds to a limit of quantification (10 × s.d.) for this HS-GC method of 1 mg dl^{-1}. The accuracy of the method was controlled by analysing known-strength standards purchased from Merck (Darmstadt, Germany) with target concentrations of ethanol corresponding to 50, 100, and 150 mg dl^{-1}.

Pharmacokinetics of ethanol

Concentration-time profiles of ethanol were plotted for the data collected from five experimental sessions. The peak BAC and the time of reaching the peak after the start of alcohol dosing were noted and the area under the concentration-time profiles (AUC) were determined by the linear trapezoidal method from 0–210 min [18]. Because ethanol metabolism exhibits saturation-type kinetics and is not a simple first-order elimination process, bioavailability cannot be calculated in the usual way as the ratio of AUC after peroral and intravenous administration [19]. Nevertheless, AUC is still a relevant parameter for comparing the different treatments provided the dose of ethanol administered is the same. The AUC gives an indication of the amount of ethanol reaching the systemic circulation after the various treatments.

The peak BAC and AUC resulting from the different treatments were compared by applying a one-way repeated measures analysis of variance (ANOVA) or by a paired *t*-test when two treatments were compared (SigmaStat, Jandel Statistics Software, Erkrath, Germany). When the dose of ethanol was ingested on an empty stomach or given by i.v. infusion, the disappearance rate of ethanol from blood was calculated from the slope of the postpeak disappearance phase assuming a zero-order elimination kinetics at BAC above 10–20 mg dl^{-1} [8]. Under these conditions, the y-intercept (C_o) and the apparent volume of distribution of ethanol (V_d) were also calculated in the usual way [8, 18]. However, when ethanol was consumed after eating food, the peak BAC for the individual subjects were often less than 10–15 mg dl^{-1} and the concentration-time curves were highly variable. Sometimes a secondary peak appeared several hours after the end of drinking. This made it impossible to fit curves and calculate elimination rate constants for individual subjects when ethanol was consumed after food.

Results

Figure 1 shows the individual blood-ethanol profiles after eating high-fat, high-protein or high-CHO meals before drinking the small dose of ethanol (0.30 g kg^{-1}). Figure 1 also shows the BAC profiles for the control conditions when ethanol was ingested on an empty stomach (p.o. fasting) or given by i.v. infusion. When the ethanol was consumed after eating a meal, regardless of the macronutrients present, there were large interindividual variations in the shapes of the curves which precluded any detailed pharmacokinetic analysis. Instead, the peak BAC, the time required to reach the peak, and the AUC were evaluated (Table 1). Figure 1 also shows mean blood-ethanol curves resulting from the different treatments making it easier to see the dramatic effect of drinking ethanol after eating a meal compared with i.v. infusion (100% availability). Systemic availability of ethanol, as reflected in peak BAC and AUC, was diminished even when the ethanol was consumed on an empty stomach, compared with i.v. infusion of the same dose.

Table 1 compares peak BAC and AUC when ethanol (0.30 g kg^{-1}) was ingested after the meals and after an overnight fast and also after i.v. infusion. The observed

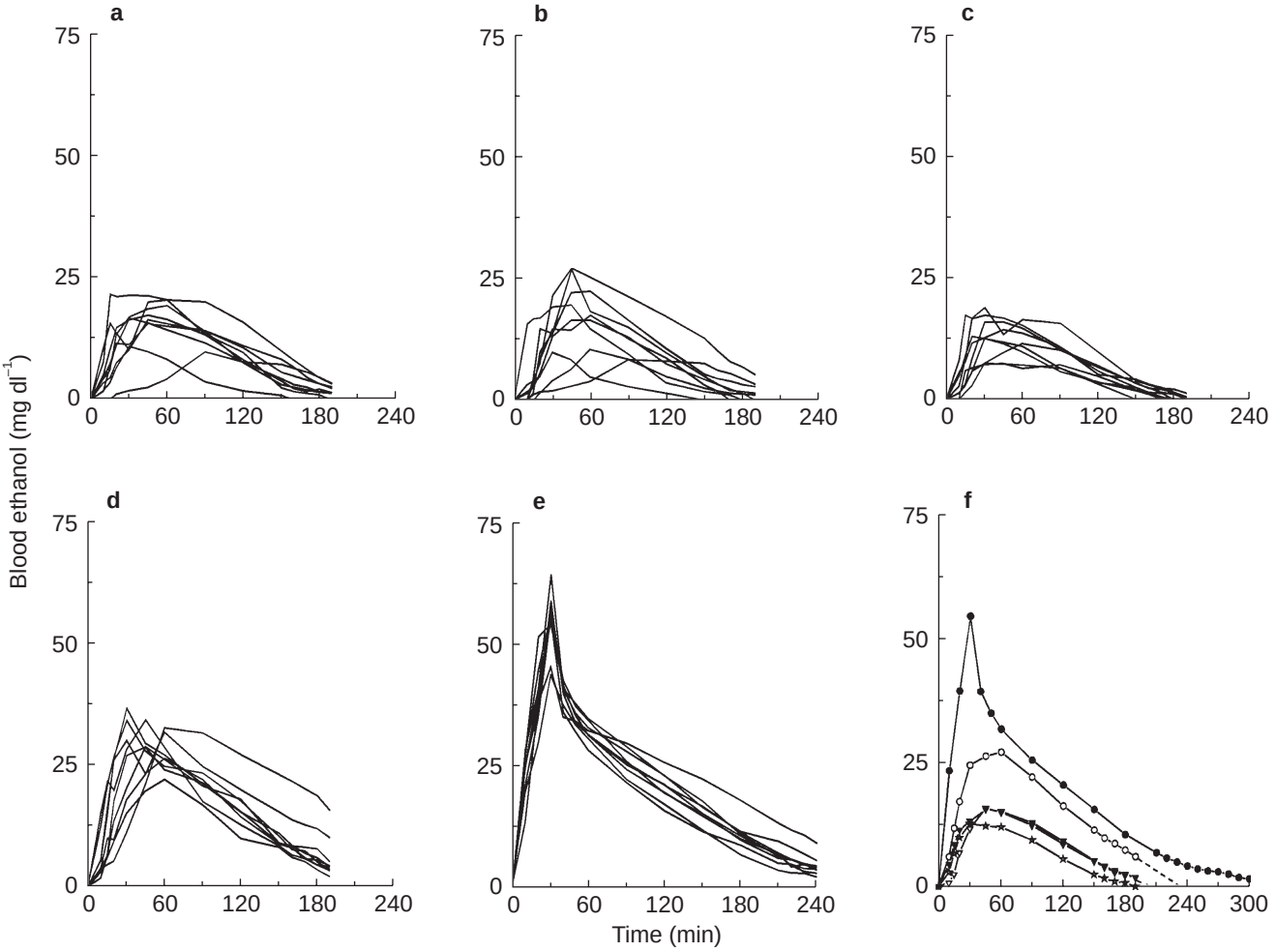

Figure 1 Concentration-time profiles of ethanol for nine healthy men after 0.30 g ethanol kg^{-1} body weight in 15 min under different conditions; (a) fat meal, (b) carbohydrate (CHO) meal, (c) protein meal, (d) fasting (empty stomach), (e) intravenous (i.v.) infusion over 30 min. Plot (f) shows the mean ($n=9$) blood-ethanol curves for the different conditions (● i.v., ○ fasting, ▼ fat meal, ▽ CHO meal, ∗ protein meal).

differences were statistically highly significant ($F=98.7$ for peak BAC and $F=88.9$ for AUC, $P<0.001$) and the power of the test *a posteriori* was 1.0. However, the differences in peak BAC and AUC did not reach statistical significance when the high-fat, high-CHO, and high-protein meals were compared separately ($F=2.22$ for peak BAC and $F=2.42$ for AUC, $P>0.05$). But these results should be interpreted with caution because the test's power calculated *a posteriori* to reveal a significant differences was relatively low being 0.22 for peak BAC and 0.25 for AUC.

The interindividual variability (CV%) in peak BAC and AUC was greatest when the ethanol was consumed after food compared with empty stomach (p.o. fasting) or i.v. infusion (Table 1). The pseudolinear disappearance phases (k_o) after i.v. infusion of ethanol was 9.8 ± 1.2 mg dl^{-1} h^{-1} and this was not significantly different from the p.o. fasting conditions, 10.3 ± 1.8 mg dl h^{-1} (95% confidence interval (CI) for the mean difference was −2.27–1.25). No significant differences were observed for C_o when i.v. infusion and p.o. fasting conditions were compared (40 ± 3.9 mg dl^{-1} (i.v.) and 37 ± 4.9 mg dl^{-1} (p.o. fasting); 95% CI for mean difference was −1.6–7.0). Neither was V_d significantly different, being 0.75 ± 0.08 l kg^{-1} for i.v. compared with 0.81 ± 0.11 l kg^{-1} for p.o. fasting; 95% CI for difference was −0.154–0.033.

Discussion

The impact of the composition of a meal in terms of the amounts of fat, protein, and carbohydrate present and whether this might influence the pharmacokinetics of a moderate dose of ethanol has not been studied in a systematic way. We found that drinking ethanol (0.30 g kg^{-1}) after eating a meal, regardless of the nutritional composition, caused a pronounced lowering of the peak BAC and a marked decrease in AUC compared with drinking on an empty stomach or i.v. administration. The rate of disposal of ethanol was boosted when there was food in the stomach because the time required to eliminate ethanol from the blood was shortened by 1–2 h compared with drinking on an empty stomach or after i.v. infusion (Figure 1). This points either to swifter metabolism of ethanol in the fed state or that part of the dose becomes metabolized before it reaches the systemic circulation, e.g. owing to first-pass metabolism (first pass metabolism).

Studies have shown that the magnitude of first pass metabolism seems to be greatest when the absorption phase is slow and more prolonged and also when small doses of ethanol (0.15–0.30 g kg^{-1}) are consumed after eating food [20, 21]. If the rate of transport of ethanol to the liver is slow and variable, metabolizing enzymes will not be saturated

Table 1 Comparison between peak BAC, time to peak, and area under the curves after 0.30 g kg^{-1} body weight was consumed after eating a meal with high-fat, high-carbohydrate (CHO), or high-protein content but having a similar calorific value. The same dose of ethanol was also ingested on an empty stomach (p.o. fasting) or by intravenous (i.v.) infusion.

Test conditions	*Energy content (percent fat, CHO, protein)*	*Peak BAC (mgdl^{-1}) (CV%)*	*AUC (mgdl^{-1} min) (CV%)*	*t_{max} (min) (range)*
High-fat meal	2908 Kj (fat 55%, CHO 33%, protein 12%)	16.6 ± 4.0, (24%)	1767 ± 549, (31%)	30–90
High-CHO meal	2924 Kj (fat 9%, CHO 86%, protein 6%)	17.7 ± 7.1, (40%)	1619 ± 760, (47%)	30–90
High-protein meal	3188 kJ (fat 24%, CHO 45%, protein 31%)	13.3 ± 4.0, (30%)	1270 ± 406, (32%)	30–60
ANOVA 3-treatments	DF = 2 and 17	F = 2.22[1] s.d.$_{res}$ = 4.4	F = 2.42[2] s.d.$_{res}$ = 492.5	—
p.o. fasting	empty stomach	30.8 ± 4.3, (14%)	3210 ± 527, (16%)	30–60
i.v. infusion	empty stomach	54.3 ± 6.4 (12%)	4786 ± 446 (10%)	30
ANOVA 5-treatments	DF = 4 and 32	F = 98.7[3] s.d.$_{res}$ = 5.1	F = 88.9[3] s.d.$_{res}$ = 465.2	—

Abbreviations; BAC = blood-alcohol concentration, AUC = area under the curve, values are mean ± s.d. for n = 9 subjects in each group, CV% = coefficient of variation (s.d./mean × 100), ANOVA = analysis of variance, DF = degrees of freedom; s.d.$_{res}$ = residual s.d. for repeated measures ANOVA.
[1]power of test (P = 0.05) = 0.221 [2]power of test (P = 0.05) = 0.251 [3]power of test (P = 0.05) = 1.0.

allowing some of the ethanol to become cleared as quickly as it is absorbed into the portal circulation. The K_m for class I human ADH, according to *in vitro* experiments, ranges from 1 to 10 mg dl^{-1} [22]. By comparison, studies *in vivo* give average values for K_m and $V_{\max}$ for the elimination kinetics of ethanol as 6.7 mg dl^{-1} and 18.1 mg dl^{-1}, respectively [23]. With low concentrations of ethanol in portal venous blood, the operation of Michaelis-Menten elimination kinetics suggests part of the dose is cleared before reaching the systemic circulation. Furthermore, if the rate of absorption of ethanol from the stomach is slower than the rate of elimination owing to metabolism and excretion processes, it is possible that the BAC profile might show a declining phase even if ethanol remains unabsorbed in the stomach [24].

Accordingly, another mechanism that could explain the abnormally low BAC profiles observed when ethanol is taken after food is a two-pool absorption hypothesis [10, 25]. With food in the stomach, a part of the ingested dose of ethanol becomes trapped or bound to constituents of the meal [25]. However, another part of the dose (free-pool of ethanol) is available for immediate absorption, which explains the initial rise in BAC and early occurring peak. The ethanol derived from the bound-pool becomes released slowly over a long period of time and, provided that the peripheral BAC remains low so that the hepatic ADH is not fully saturated, all the ethanol released from the bound-pool is cleared during the first passage of portal venous blood through the liver. In one subject, we observed a secondary peak in the BAC arising about 2 h after drinking ended. Cortot *et al.* [26] reported a slow and protracted absorption of ethanol from the human stomach when a homogenized meal was given mixed with 1 g kg^{-1} ethanol. They estimated that 73% of the dose of ethanol was absorbed from the stomach over several hours after administration and only 27% from the duodenum. This supports the notion of a bound pool of alcohol in the stomach even 3 h or more after administration [25, 26].

The rate of disappearance of ethanol from blood in the fasting state and after i.v. infusion was relatively slow (10 mg dl^{-1} h^{-1}), which is considerable less than the mean of 15 mg dl^{-1} h^{-1} often cited in the literature for moderate drinkers [4, 8]. It seems that food deprivation for 10–12 h is sufficient to decrease the activity of alcohol metabolizing enzymes and this accounts for the slower rate of disappearance of ethanol from blood [27]. In some studies, CHO enriched food proved more effective than fat or protein in accelerating the metabolism of ethanol but the mechanism for this finding was not elucidated [28].

Our results confirm and extend earlier work on food-induced effects on the bioavailability of ethanol although we failed to find any major significance of the various macronutrients (fat, CHO, protein) on the pharmacokinetics of ethanol when normally available foodstuffs were eaten. The protein-rich meal tended to produce lower BAC profiles than the fat or CHO treatments, but the differences observed were not statistically significant. The BAC profiles after the CHO-rich meal showed most interindividual variation. Time-response studies of the effects of food on BAC profiles have apparently not been reported, although

we noted a more pronounced influence the shorter the time between eating a meal and drinking the ethanol (unpublished work).

The implications of food–alcohol interactions should not be overlooked in forensic casework when BAC must be estimated from a particular set of drinking conditions. The possibility of first pass metabolism should be considered especially after small doses are consumed together with or after a meal. A slow and variable absorption of alcohol in the fed-state means that some of the ethanol can be cleared by FPM owing to the Michaelis-Menten elimination kinetics of ethanol. If the concentrations of ethanol in the peripheral venous blood remain low and close to the K_m of ADH, some of the ingested ethanol will be cleared during the first-passage of portal blood through the liver. Under these conditions, peripheral venous BAC will be less then expected for the administered dose and exhibit large individual variations. Factors influencing liver blood flow, such as eating will influence the resulting peak BAC and AUC when hepatic ADH is not saturated, i.e. at low concentrations in portal blood [29, 30].

We conclude that the presence of food in the stomach before drinking has a major influence on the peak BAC and AUC. Both of these parameters are lowered considerably when compared with drinking on an empty stomach (peroral fasting) or parenteral (i.v.) administration. The composition of the meal, whether high-fat, high-carbohydrate or high-protein is not so important in this respect. The amount of ethanol reaching the systemic circulation is apparently less, but this observation is confounded by first pass metabolism as one consequence of the protracted absorption and Michaelis-Menten kinetics.

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References

1 Jones AW. *Forensic science aspects of ethanol metabolism*. In: Forensic Science Progress, Vol. 5, Springer-Verlag, Berlin 1991, pp. 33–89.

2 Jones AW, Jönsson KÅ, Neri A. Peak blood-ethanol concentration and the time of its occurrence after rapid drinking on an empty stomach. *J Forens Sci* 1991; **36**: 376–385.

3 Wagner JG, Wilkinson PK, Ganes DA. Estimation of the amount of alcohol ingested from a single blood alcohol concentration. *Alc Alcohol* 1990; **23**: 379–384.

4 Al-Lanqawi Y, Moreland TA, McEwen J, Halliday F, Durnin CJ, Stevenson IH. Ethanol kinetics: extent of error in back extrapolation procedures. *Br J Clin Pharmacol* 1992; **34**: 316–321.

5 Horowitz M, Maddox A, Bochner M, *et al*. Relationship between gastric emptying of solid and caloric liquid meals and alcohol absorption. *Am J Physiol* 1989; **257**: G291–G298.

6 Fraser AG, Rosalki SB, Gamble GD, Pounder RE. Inter-individual and intra-individual variability of ethanol concentration-time profiles: comparison of ethanol ingestion before or after an evening meal. *Br J Clin Pharmacol* 1995; **40**: 387–392.

7 Welling PG. Pharmacokinetics of alcohol following single low doses to fasted and non-fasted subjects. *J Clin Pharmacol* 1977; **17**: 199–206.

8 Widmark EMP. *Die theoretischen Grundlagen und die praktische Verwendbarkeit der gerichtlich-medizinischen Alkoholbestimmung*, Berlin, Urban & Schwarzenberg 1932, 1–140. (Translation to English and entitled 'Principles and Applications of Medicolegal Alcohol Determinations,' Davis, California, Biomedical Publications 1981, 1–163.

9 Levitt MD, Levitt DG. The critical role of the rate of alcohol absorption in the interpretation of studies purporting to demonstrate gastric metabolism of ethanol. *J Pharmacol Exp Ther* 1994; **269**: 297–304.

10 Jones AW, Jönsson KÅ. Food-induced lowering of peak blood-alcohol concentration and increased rate of alcohol elimination immediately after a meal. *J Forens Sci* 1994; **39**: 1084–1093.

11 Wilkinson PK, Sedman AJ, Sakmar E, Lin YJ, Wagner JG. Fasting and non-fasting blood ethanol concentration following repeated oral administration of ethanol to one adult male subject. *J Pharmacokinet Biopharm* 1977; **5**: 41–52.

12 Levitt MD. Review article: Lack of clinical significance of the interaction between H_2-receptor antagonists and ethanol. *Aliment Pharmacol Ther* 1993; **7**: 131–138.

13 Gentry RT, Baraona E, Lieber CS. Gastric first pass metabolism of ethanol. *J Lab Clin Med* 1994; **123**: 21–26.

14 Sato N, Kitamura T. First-pass metabolism of ethanol: An overview. *Gastroenterology* 1996; **111**: 1143–1144.

15 Ammon E, Schäfer C, Hofmann U, Klotz U. Disposition and first-pass metabolism of ethanol in humans: Is it gastric or hepatic and does it depend on gender? *Clin Pharmacol Ther* 1996; **59**: 503–513.

16 Jones AW, Schuberth J. Computer-aided headspace gas chromatography applied to blood-alcohol analysis; Importance of online process control. *J Forens Sci* 1989; **34**: 1116–1127.

17 Jones AW. Limits of detection and quantitation of ethanol in specimens of whole blood from drinking drivers analyzed by headspace gas chromatography. *J Forens Sci* 1991; **36**: 1277–1279.

18 Roland M, Tozer TN. *Clinical pharmacokinetics; Concepts and applications*. Philadelphia, Lea & Febiger 1980.

19 Tozer TN, Rubin GM. *Saturable kinetics and bioavailability determination in pharmacokinetics, Regulatory, Industrial, Academic Perspectives*, Vol 33, Drugs and the Pharmaceutical Sciences, eds Welling PG, Tse FLS, New York, Marcel Dekker Inc. 1988, 473–513.

20 Fressa M, Padova DI, Pozzato C, Terpin G, Baraona M & Elieberigh CS. Blood alcohol levels in women; The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *N Engl J Med* 1990; **322**: 95–99.

21 Seitz HK, Egerer G, Simanowski UA, *et al*. Human gastric alcohol dehydrogenase activity; effect of age, sex, and alcoholism. *Gut* 1993; **34**: 1433–1437.

22 Hittle JB, Crabb DW. The molecular biology of alcohol dehydrogenase: Implications for the control of alcohol metabolism. *J Lab Clin Med* 1988; **112**: 7–15.

23 Wagner JG, Wilkinson PK, Ganes DA. Parameters V_{max} and K_m for elimination of alcohol in young male subjects following low doses of alcohol. *Alc Alcohol* 1989; **24**: 555–564.

24 Haggard HG, Greenberg LA. Studies on the absorption, distribution and elimination of alcohol. V. The influence of glycocoll upon the absorption of alcohol. *J Pharmacol Exp ther* 1948; **68**: 482–493.

25 Schultz J, Weiner H, Westcott J. Retardation of ethanol

absorption by food in the stomach. *J Stud Alc* 1980; **41**: 861–870.
26 Cortot A, Jobin G, Ducrot F, Aymes C, Giredeaux V, Modigliani R. Gastric emptying and gastrointestinal absorption of alcohol ingested after a meal. *Dig Dis Sci* 1986; **31**: 343–348.
27 Bode JC, Thiele D. Hemmung des Åthanolabbaus bein Menschen durch Fasten: Reversibilität durch Fructose-Infusion. *Deutsh med Wochen* 1975; **100**: 1849–1851.
28 Rogers JO, Smith J, Starmer GA, Whitfield J. Differing effects of carbohydrate fat and protein on the rate of ethanol metabolism. *Alc Alcohol* 1987; **22**: 345–353.
29 Melander O, Liden A, Melander A. Pharmacokinetic interactions of alcohol and acetylsalicylic acid. *Eur J Clin Pharmacol* 1995; **48**: 151–153.
30 Svensson CK, Edwards DJ, Maurietto PM, *et al*. Effect of food on hepatic blood flow: Implications in the 'food effect' phenomenon. *Clin Pharmacol Ther* 1983; **34**: 316–323.

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