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Inter-individual and intra-individual variability of ethanol concentration-time profiles: comparison of ethanol ingestion before or after an evening meal

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1 The magnitude of the variability of ethanol absorption is an important factor for studies that seek to determine the significance of potential interactions between ethanol and drugs. The aim of this study was to determine the extent of inter- and intra-individual variability of ethanol concentration-time profiles in fasted and fed subjects.

2 Twenty-four healthy male subjects were randomized to receive ethanol 0.3 g kg^{-1} before an evening meal on two study days and ethanol 0.3 g kg^{-1} after an evening meal on two study days. Plasma ethanol concentrations were measured at intervals from 0–240 min.

3 There were significant differences in the mean area under the ethanol concentration-time curve (AUC), the mean peak ethanol concentration (C_{max}), the mean ethanol elimination slope and the time to peak ethanol concentration between the fed and fasted subjects. There were no significant differences between the first and second study days for either fed or fasting subjects for all parameters.

4 There was no statistically significant difference in inter- or intra-subject variance between fed and fasted studies although the coefficients of variation (standard deviation expressed as a percentage of the mean) for the differences between the first and second study day were higher for fed studies.

5 The large inter- and intra-individual variability of alcohol absorption for both fasted and fed subjects must be considered in the design of alcohol-drug interaction studies.

Keywords ethanol variability absorption food

Introduction

A large number of studies has been conducted to investigate the absorption and disposition of ethanol [1]. It is clear that many different factors affect ethanol pharmacokinetics including gender [2], food (composition of the meal and timing of the meal with respect to alcohol ingestion) [3–7], genetics [8, 9], the type of beverage and concentration of alcohol [10, 11], the time of day of ethanol ingestion and the extent of first pass metabolism [12, 13]. Substantial inter-subject variability has been reported in several studies in the fasting state, but there are few data on the effect of food on inter- and intra-subject variability [14–17].

Delayed alcohol absorption after food ingestion is probably related to slower gastric emptying [5–7]. In the fed state, slower gastric emptying results in a slower rate of delivery of alcohol to the duodenum and small intestine. This consequent decrease in absorption rate of alcohol results in more effective extraction of alcohol by the liver (increased first pass metabolism) [18]. There is considerable variability in the rate of gastric emptying following a meal and this would be expected to affect variability of ethanol bioavailability after a meal [19].

The aim of this study was to determine the extent of the inter- and intra-individual variability and to

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test whether there were any differences in inter- or intra-individual variability for either pre- or post-prandial ethanol ingestion.

Methods

Study design and subjects

A randomised four-arm cross-over study was used to compare inter- and intra-subject variability of ethanol absorption before and after food. Twenty-four healthy male volunteers, aged between 19 and 27 years, median 77.5 kg weight (range 65–109 kg), with normal biochemistry and haematology profiles were recruited into the study. Twenty subjects were European and four subjects were Asian. Subjects were excluded from taking part if they were taking any concurrent medication. In addition, subjects were asked to abstain from alcohol for 48 h prior to each study. The study was approved by the Ethics Committee of the Hampstead Health Authority, London.

There were four study days at weekly intervals; each subject received ethanol before the evening meal on two occasions and after the evening meal on two occasions. The timing of the ethanol dosing (before or after food) on each study day was allocated using a latin square design to balance for any order effect. The first fasting study for a subject is termed Study 1 and the second fasting study for a subject is termed Study 2—the same terms are used for the fed studies. On each study day subjects consumed 0.3 g kg^{-1} of ethanol made up to a volume of 200 ml with orange juice, either 1 h before the evening meal or 1 h after the meal, according to the allocation schedule.

The procedure for each study day was similar to previous studies on the effect of histamine H_2-receptor antagonists on ethanol bioavailability [20–23]. On each study day subjects attended at 17.15 h and an intravenous cannula was inserted into a forearm vein and kept patent with heparinised saline. At 17.30 h subjects were given 200 ml of orange juice. At 18.30 h subjects ate a standard meal (details previously presented [20–23]) consumed over 20 min. One hour after commencing the evening meal (19.30 h) subjects were given a second drink of orange juice (200 ml). Depending on the allocation schedule, either the orange juice 1 h before or 1 h after the meal contained 0.3 g kg^{-1} of ethanol—both drinks were taken over 1–2 min.

Venous blood samples (2 ml) were collected 5 min prior to ingestion of ethanol and 5, 10, 15, 20, 25, 30, 40, 50, 60, 80, 100, 120, 140, 160, 180, 210, 240 min after ingestion. Before each blood sample was taken, 2 ml of fluid was withdrawn through the cannula and discarded. The samples were collected in a sodium fluoride/glucose screw top tube, filled to the top to eliminate air and stored overnight at 4° C before centrifugation and analysis the following day.

Plasma samples were analysed by using the Sigma Diagnostics Alcohol Procedure No 332-UV. Alcohol dehydrogenase is used to catalyse the oxidation of ethanol to acetaldehyde with simultaneous reduction of nicotinamide adenine dinucleotide (NAD) to NADH. The consequent increase in absorbence is directly proportional to the ethanol concentration in the sample [24, 25]. Each 100 µl plasma sample was analysed in duplicate with two standards (40 mg dl^{-1}) run at the beginning and end of each subject's samples. Analysis was performed using Encore analysers (Baker Instrument Corporation, Allentown, Pennysylvania, USA). The analyst estimated the plasma ethanol concentration without knowledge of the dosing allocation received by each subject.

The mean of each set of duplicate measurements was taken as the plasma ethanol concentration at that time. The area under the plasma ethanol concentration-time curve from time zero until the time of the last value recorded (AUC) was determined using a linear trapezoidal method. Peak plasma ethanol concentration (C_{max}) and time to peak concentration (t_{max}) were taken directly from the concentration data. Zero-order elimination was assumed in the post-absorptive phase. The elimination slope for each subject was calculated from the near-linear portion of the absorption profiles. The number of data points included in this analysis differed depending on when the peak ethanol concentration was reached.

Statistical methods

The intra-individual variability before or after a meal was tested by calculating the coefficient of variation for the differences between the first and second study day. The variance for AUC, peak ethanol concentration and elimination slope were calculated for studies 1 and 2 for both fed and fasted subjects. The variance of the difference between study 1 and 2 was also calculated for all parameters (SAS) [26]. Homogeneity of variance was tested using a two-tailed *F*-test ($\alpha = 0.05$).

Results

Two subjects did not complete two fasted and two fed studies and were excluded in the analysis.

Fasting vs *fed studies*

The overall mean C_{max} when ethanol 0.3 g kg^{-1} was given before a meal was significantly greater than the mean C_{max} when ethanol was given 1 h after the meal (39.9 mg dl^{-1} *vs* 21.3 mg dl^{-1} respectively, $P < 0.0001$). The overall mean AUC when ethanol was given before a meal was also significantly greater than the mean AUC when ethanol was given after the meal (54.8 mg dl^{-1} h *vs* 33.6 mg dl^{-1} h respectively, $P < 0.0001$). The overall mean AUC and the mean C_{max} for subjects given ethanol after an evening meal were similar to previous studies of the same dose of ethanol given in similar conditions [20, 21]. The mean slope of the rectilinear elimination phase was

171.0 mg l^{-1} h^{-1} for fasted subjects and 92.2 mg l^{-1} h^{-1} for fed subjects ($P < 0.0001$).

The mean ethanol concentration-time curve for study 1 and 2 for fed and fasted studies is shown in Figure 1. The mean and standard deviation for all parameters for study 1 and study 2 for the fed and fasted studies are shown in Table 1a. There was no significant difference for any of the variables between first and second study days, where the subjects were either fasting or fed ($P > 0.05$).

Intra- and inter-subject variance

The coefficient of variation (standard deviation expressed as a percentage of the mean) for intra-subject variability for area under curve, peak ethanol concentration, slope of the rectilinear elimination phase and time to peak ethanol concentration was greater in the fed state (Table 1b). There was no statistically significant difference for intra- and inter-subject variance between fed and fasted studies (two-tailed F-test to assess the homogeneity of the variance). The high level of within subject variability is well illustrated using Bland & Altman plots [27] (Figure 2).

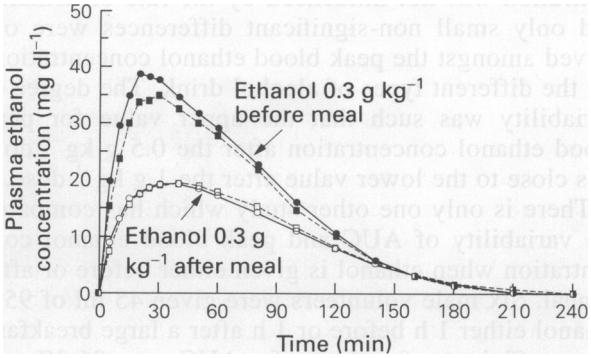

Figure 1 The mean plasma ethanol concentration-time curves for study 1 (—) and study 2 (---) for fasted and fed subjects.

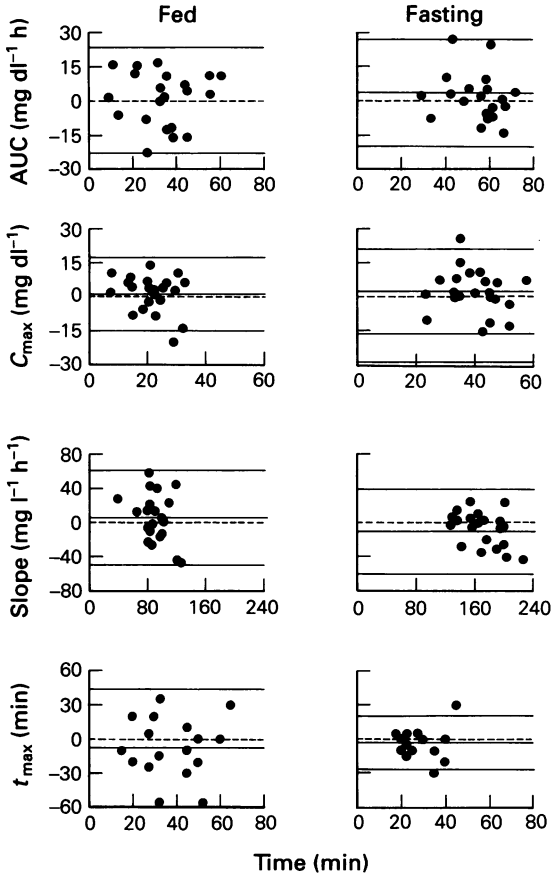

Figure 2 The within subject variability is shown using Bland & Altman plots [27]. The x axis is the average value for each parameter over the two studies. The y axis is the value of the difference of the second study from the first study. Also shown are the mean difference (from Table 1a) and the limits of agreement (± 1.96* s.d.).

Table 1 a) Mean values (± s.d.) for AUC, peak concentration, slope and time to peak concentration when ethanol is given before or after a standard meal ($n = 22$) and b) within and between subject coefficients of variation for AUC, peak concentration, slope and time to peak concentration when ethanol is given before or after a standard meal

a	*Fed*			*Fasted*			
	Study 1	*Study 2*	*Difference**	*Study 1*	*Study 2*	*Difference**	*Fed-Fasted***
AUC (mg dl^{-1} h)	34.1 ± 15.0	33.7 ± 15.2	0.36 ± 11.9	56.6 ± 11.9	53.1 ± 14.6	3.5 ± 11.9	−20.9 ± 12.5
C_{max} (mg dl^{-1})	22.0 ± 7.4	20.9 ± 9.2	1.11 ± 8.3	41.0 ± 9.5	38.8 ± 10.8	2.2 ± 9.5	−18.5 ± 8.3
Slope (mg l^{-1} h^{-1})	94.8 ± 19.4	89.6 ± 27.2	5.2 ± 28.2	165.5 ± 26.0	176.4 ± 34.1	−10.9 ± 25.5	−78.8 ± 25.4
t_{max} (min)	33.6 ± 17.5	40.9 ± 20.2	−7.3 ± 26.2	25.9 ± 9.8	29.1 ± 9.8	−3.2 ± 11.9	9.8 ± 16.2

b	*Fed*		*Fasted*	
	Between subject CV	*Within subject CV*	*Between subject CV*	*Within subject CV*
AUC	44%	35%	21%	22%
C_{max}	34%	38%	23%	24%
Slope	20%	30%	16%	15%
t_{max}	52%	70%	38%	43%

*All $P > 0.05$, **All $P < 0.009$, ***$P = 0.03$.
There were no differences in between- or within-subject variances between fed and fasted studies (two-tailed F-test, all $P > 0.17$).

Discussion

There was considerable inter- and intra-subject variability of ethanol bioavailability for both fasted and fed subjects. Variability in ethanol concentrations, both within and between subjects, was greater if ethanol was taken after a meal when assessed by coefficient of variation but there was no statistically significant difference in absolute values for variance. The overall means for C_{max} and AUC were greater when ethanol was given before the evening meal, similar to previous studies [6, 7, 28]. The difference in the slope of the rectilinear elimination phase for fed and fasted subjects probably relates to continuing absorption of ethanol at different rates during the period of time used to calculate the elimination slope.

The effect of food on inter- and intra-individual variability was not as great as expected and other factors should be considered. For the differences between individuals, the genetic control of ethanol metabolism has been suggested by several twin studies which revealed less variability in ethanol metabolism within monozygotic than within dizygotic twins [8]. However, most studies have ascribed a small proportion of the total inter-individual variability to genetic factors and a much larger portion to environmental factors [9].

Intra-subject variability is probably determined by the day to day variation in gastrointestinal function—particularly gastric emptying, intestinal transit time and portal blood flow. There is some information on the effect of gastric emptying on alcohol absorption but less is known of inter- and intra-subject variability of intestinal transit time and portal blood flow [29].

Small variations in the composition of the meal can have very significant effects on alcohol absorption [30]. Great inter- and intra-subject variability in gastric emptying has been demonstrated even with a strictly standardized protocol of meals [19, 29, 31]. Gastric emptying has a marked effect on absorption of most drugs because it governs the access of the drug to the main absorptive surface, the small intestine [32]. The area under the plasma ethanol concentration-time curve has been shown to correlate closely with the half-time emptying of liquids from the stomach [33, 34]. An increased rate of delivery of alcohol to the small intestine is likely to be the reason for the increased AUC in patients who have had a gastrectomy or after intra-duodenal instillation of ethanol [35]. Intravenous erythromycin increases the AUC of alcohol in keeping with the drug's prokinetic effect of increasing the rate of gastric emptying [34].

Ethanol pharmacokinetics have been extensively investigated but few studies have investigated intra-subject variability. Al-Lanqawi *et al.* [14] studied five healthy male volunteers on four occasions who were given 0.7 g kg^{-1} of ethanol in the fasting state. Plasma ethanol concentration was measured over the following 9 h. The parameters with greatest variability were t_{max} and C_{max} with the least variability for the elimination slope. Inter-individual variability was greater than intra-individual variability. The authors concluded that C_{max} and t_{max} were significantly influenced by changes in absorption and that this factor accounted for most variability. Similar results were reported by Jones *et al.* [36] who studied 12 healthy men given 0.8 g kg^{-1} of ethanol after an overnight fast on four occasions. Passananti *et al.* [15] studied eight male volunteers who received 1 ml kg^{-1} of 95% ethanol (approximately 0.8 g kg^{-1}) after an overnight fast on 4 successive weeks. They found a high degree of reproducibility for the elimination slope of blood ethanol; the coefficient of variation ranged from 3 to 12% for each subject. The consumption of food before ethanol administration was reported to increase variability but the data were not published. O'Neill *et al.* [10] studied 64 volunteers (four groups of 16) who had four different types of alcohol in a parallel design; either beer, champagne, straight whisky or whisky mixed with non-alcohol beverage. Each group was studied with two different doses of ethanol (0.5 or 1 g kg^{-1}) at two different rates of ingestion of ethanol. Mean peak ethanol alcohol concentration was not influenced by the rate of drinking and only small non-significant differences were observed amongst the peak blood ethanol concentrations for the different types of alcohol drink. The degree of variability was such that the upper value for peak blood ethanol concentration after the 0.5 g kg^{-1} dose was close to the lower value after the 1 g kg^{-1} dose.

There is only one other study which has compared the variability of AUC and peak blood ethanol concentration when ethanol is given either before or after a meal. Six male volunteers were given 45 ml of 95% ethanol either 1 h before or 1 h after a large breakfast. The coefficients of variation for AUC were 26.3% and 22.8% in the fasted or fed states respectively; the coefficients of variation for peak ethanol concentration were 31.2% and 19.5%, respectively [6].

The implications of the greater inter- and intra-individual variability are several. Firstly, the practice of back-extrapolation to approximate the blood ethanol concentration at the time of a motor vehicle accident may be unreliable [37]. The low doses of ethanol used in this study does not permit comment on the medico-legal issues. The difference in elimination slope between fasted and fed subjects emphasizes the limitation of calculations that assume zero-order kinetics. Back-tracking is not possible during periods of possible continuing alcohol absorption—this is relevant to the context of most social drinking, where alcohol is consumed intermittently over a long period of time together with food.

The second implication of the large inter-subject variability is that any study which seeks to determine the effect of any drug on ethanol metabolism must have sufficient numbers and a careful design to avoid an incorrect conclusion. A cross-over design with each subject acting as his own control is preferable, to avoid ascribing an effect to treatment rather than to chance because of the great inter-individual variability of alcohol absorption. Intra-subject variability

is amost as great as inter-subject variability and wrong conclusions could easily be made if the power of the study is insufficient to take into account this variability. We chose to study the bioavailability of a relatively small dose of alcohol, that is 0.3 g kg^{-1} of body weight, as these data have relevance to much of the controversy on the potential effect of histamine H_2-receptor antagonists on alcohol bioavailability [20, 21, 38, 41]. Many published studies on this issue have used subject numbers that are too small to achieve reliable results [39, 40].

In summary, there is considerable inter- and intra-individual variability in ethanol bioavailability when ethanol 0.3 g kg^{-1} is given either before or after an evening meal. Absolute values of variance are similar for fasted and fed subjects, but are greater for fed subjects when variability is expressed as coefficients of variation. The statistically significant changes of the mean peak ethanol concentration reported after dosing with H_2-receptor antagonists [40–41] are trivial compared with the day-to-day variation in alcohol absorption in an individual.

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