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J. Clin. Pharmacol. 2001; 41; 1345

Effect of Food and Food Composition on Alcohol Elimination Rates in Healthy Men and Women

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Several studies have evaluated the effect of food on alcohol pharmacokinetics; however, most studies have used oral alcohol administration, which cannot separate the influence of food on absorption from its influence on alcohol elimination. Alcohol clamping uses intravenous alcohol and provides a direct measure of the alcohol elimination rate (AER). Two studies, using alcohol clamping at 50 mg%, were conducted to investigate the effect of food and food composition on AER (g/h) in healthy men and women. In the first study, 20 subjects underwent two clamping sessions, one after a 12-hour fast and another 1 hour after consuming a 530-calorie breakfast. In the second study, 8 subjects underwent four clamping sessions: one after a 12-hour fast and, in each of three "fed" sessions, 1 hour after a 550-calorie high-fat, high-protein, or high-carbohydrate breakfast. Comparison of AERs from the first study showed an average 25% increase following food compared to that following fasting. Men showed significantly higher AERs compared to women; however, the food effect was similar in both genders. In the second study, the AER showed a significant average 45% increase following the meal, regardless of composition, compared with that following fasting. These findings indicate that food intake results in increased alcohol elimination rates. The increase was similar for meals of different compositions, suggesting that the food effect is not due to specific interactions with meal constituents. Probable mechanisms for the increased alcohol elimination include food-induced increases in hepatic blood flow and in the activity of alcohol-metabolizing enzymes.

Journal of Clinical Pharmacology, 2001;41:1345-1350

Several studies have investigated the effect of food on alcohol pharmacokinetics following oral ingestion and found a decrease in absorption rate and an increase in first-pass metabolism, resulting in lower and delayed peak blood alcohol levels.[1-6] Studies have also indicated an increase in the disappearance rate of alcohol after a meal.[2,5-7] However, most of these studies have employed oral alcohol administration and thus cannot reconcile the confounding effects of food on alcohol absorption from the effects of food on alcohol elimination. Breath alcohol clamping uses intravenous infusions of alcohol to achieve and maintain breath alcohol concentrations (BrAC) at a target level for prolonged periods of time.[8-10] During this steady state, the alcohol infusion rate is a direct measure of the alcohol elimination rate (AER). Studies using the BrAC clamp thus allow the evaluation of the influence of food on AER without the confounding effect on alcohol absorption.

Two studies were conducted to evaluate the effect of food and food composition on AER in healthy men and women. The objective of the first study was to evaluate the effect of food intake on AER in healthy men and women. The objective of the second study was to investigate the influence of food composition on AER.

METHODS

Study I

This was a two-session study performed in 20 subjects. In one session, subjects underwent an alcohol clamping session at 50 mg%, following a 12-hour overnight fast; in the other session, subjects underwent the same alcohol clamping procedure 1 hour following the consumption of a standard 530-calorie breakfast. Sessions were conducted in counterbalanced order across subjects. This study was approved by Indiana University's

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institutional review board and was conducted in the General Clinical Research Center (GCRC) at Indiana University Hospital.

Subjects. Subjects were 10 male and 10 female social drinkers, between 21 and 30 years of age. Subjects were determined to be of good health based on a medical history and physical examination. Subjects with a history of any *DSM-IV* diagnosis, including substance abuse, or who were taking any prescribed psychoactive medication were ineligible. All were nonsmokers. Subjects with a history of renal, cardiovascular, pulmonary, or gastrointestinal disease were excluded. Subjects who produced a nonzero BrAC or failed a physical examination for current good health on admission to the GCRC were also ineligible for the study. Females were scheduled for testing during the follicular phase of their menstrual cycle, and those with a positive urine test for β-hCG on the day of testing were excluded from the study.

Procedures. During each session, subjects were admitted to the GCRC on the evening before the day of study at 9 p.m. They signed the informed consent form and completed a brief medical history questionnaire. A negative urine β-hCG test was obtained for the female subjects. On the morning of the study, a physical examination was performed, and an IV catheter was inserted in the antecubital vein of one arm for alcohol administration.

During the fasted session, subjects started a fast from admission until the end of the alcohol clamping the following day (~15 h). During the fed session, subjects fasted overnight and received a standard breakfast consisting of two fried eggs, two pieces of bacon, two pieces of toast with jam, and 8 oz of orange juice, totaling 530 calories, at 8:00 a.m., exactly 1 hour prior to the start of the alcohol infusion. Subjects consumed the breakfast within 15 minutes.

At 9:00 a.m., subjects underwent the alcohol clamping procedure, as described in previous studies.[8,9] An oral loading dose of 95% ethanol diluted 1:4 with soda was calculated to produce a target breath alcohol concentration (BrAC) of ~40 mg% at 30 minutes based on the subject's height and weight.[11] An intravenous (IV) infusion of 6% (v/v) ethanol in Ringer's lactate was started simultaneously. Based on serial measurements of BrAC obtained every 5 minutes, the infusion rate was adjusted to maintain the BrAC at 50 mg%. A steady state was achieved when both the intravenous infusion rate and BrAC remained constant for at least 45 minutes at 50 ± 5 mg%. BrAC was determined using two identically calibrated breathalyzers (Alcosensor IV, Intoximeters, Inc., St. Louis, MO). The alcohol infusion was stopped at the end of 180 minutes, after which lunch was served. The BrAC was tracked at approximately 20-minute intervals until it fell to below 20 mg%, when subjects were discharged from the unit.

Data analysis. For each session, the AER was calculated by multiplying the concentration of the infusate by the steady-state infusion rate.

As this was a repeated-measures design, comparison of AER in the "fed" and the "fasted" state was made using two-way repeated-measures ANOVA. Gender was included as the second factor to explore any gender differences in the food effect on AER.

Study II

This was a four-session, randomized, alcohol clamping study in 8 subjects under four different conditions: (1) following a 12-hour overnight fast, (2) following a high-fat breakfast, (3) following a high-protein breakfast, and (4) following a high-carbohydrate breakfast. All breakfasts were 550 calories in content. Sessions were conducted in randomized order based on a Latin square design. This study was also approved by Indiana University's institutional review board and was conducted in the GCRC.

Subjects. Subjects were 4 male and 4 female social drinkers, between 21 and 30 years of age. Subjects were determined to be of good health based on a medical history and physical examination. All inclusion and exclusion criteria were identical to those for Study I.

Procedures. During each of the four sessions, subjects were admitted to the GCRC on the evening before the day of study at 9 p.m. Subjects signed the informed consent form and completed a brief medical history questionnaire. A negative urine β-hCG test was obtained for the female subjects. On the morning of the study, a physical examination was performed, and an IV catheter was inserted in the antecubital vein of one arm for alcohol administration.

During the fasted session, subjects started a fast from admission until the end of the alcohol clamping the following day (~15 h). During the other three sessions, subjects fasted overnight and received breakfast at 8:00 a.m., exactly 1 hour prior to the start of the alcohol infusion. For each of the three "fed" sessions, subjects received a high-fat, high-protein, or high-carbohydrate breakfast in random order. The composition and content of the meals are shown in Table I. Subjects consumed the breakfast within 15 minutes.

At 9:00 a.m., subjects underwent the alcohol clamping procedure, using the intravenous alcohol (quick-

Table I Content and Composition of Meals in Study II

	High Fat	High Protein	High Carbohydrate
Contents	2 slices wheat bread, 10 g margarine, 2 slices bacon, 2 eggs, 8 oz whole milk	1 slice wheat bread, 13 g peanut butter, 5 g margarine, 380 g egg substitute, 10 oz skim milk + 30 g milk powder	2 slices wheat bread, 5 g margarine, 2 packets jelly, 4 oz orange juice, 52 g cereal, 6 oz skim milk
Total fat (g)	33.5	12.7	6.8
Total protein (g)	20.2	60.6	13.5
Total carbohydrate (g)	37.7	50.5	111.3
% calories from fat	53	21	10
% calories from protein	27	43	10
% calories from carbohydrate	20	36	80
Total calories (Kcal)	566	557	550

clamp) protocol, as described in a previous study.[10] An intravenous (IV) infusion of 6% (v/v) ethanol in Ringer's lactate was infused to achieve and maintain a target BrAC of 50 mg%. Alcohol was infused according to an infusion profile that was based on a physiologically based pharmacokinetic model for alcohol. The profile consists of an exponentially increasing infusion rate from the start of the infusion until the target BrAC is reached, followed by an exponentially decreasing infusion rate that tapers to a constant steady-state value. This infusion profile is computed using individualized estimates of the model parameters, which are based on the subject's height, weight, age, and gender and results in the desired BrAC-time profile for each subject. Serial breathalyzer measurements allow the monitoring of BrAC levels to ensure they are constant and also enable minor adjustments to the infusion rates to overcome errors in parameter estimation and experimental variability. A steady state was achieved when both the intravenous infusion rate and BrAC remained constant for at least 45 minutes at 50 ± 5 mg%. BrAC was determined, every 2 to 10 minutes, using four identically calibrated breathalyzers (Alcosensor IV, Intoximeters, Inc., St. Louis, MO) in rotation. The alcohol infusion was stopped at the end of 180 minutes, after which lunch was served. The BrAC was tracked at approximately 20-minute intervals until it fell to below 20 mg%, when subjects were discharged from the unit.

Data analysis. For each session, the AER was calculated by multiplying the concentration of the infusate by the steady-state infusion rate.

Comparison of AER across the four sessions was made using one-way repeated-measures ANOVA. Due to the small sample size, formal analysis of gender differences was not done in this part of the study.

RESULTS

Table II shows the characteristics of the subjects in Study I. As expected, female subjects had lower body weight ($p = 0.01$) and lean body mass ($p = 10^{-8}$) than the male subjects. Figure 1 shows the mean (± *SE*) alcohol elimination rates for female and male subjects during the fasted and fed sessions. Statistical analysis revealed a significant effect of gender ($p = 0.009$) and session ($p = 0.001$) without any significant interaction. This indicates that there was a significant effect of food intake on the AER in both male and female subjects. There was an average 25% increase in AER following the intake of a 530-calorie meal compared to that following an overnight fast. The percent change in AER ranged from 9% to 49% across subjects. There was a significant effect of gender, with men showing significantly higher AERs compared to women; however, the effect of food was similar in both men and women.

Table II Study I Subject Demographics

	Females (n = 10): Mean ± *SE*	Males (n = 10): Mean ± *SE*
Age (years)	24 ± 3	25 ± 3
Height (cm)	166 ± 7	177 ± 8
Weight (kg)	72.9 ± 15.9[a]	87.7 ± 10.5[a]
Lean body mass (kg)	46.4 ± 1.8[b]	67.1 ± 1.6[b]

a. Females versus males; $p = 0.012$.
b. Females versus males; $p = 10^{-8}$.

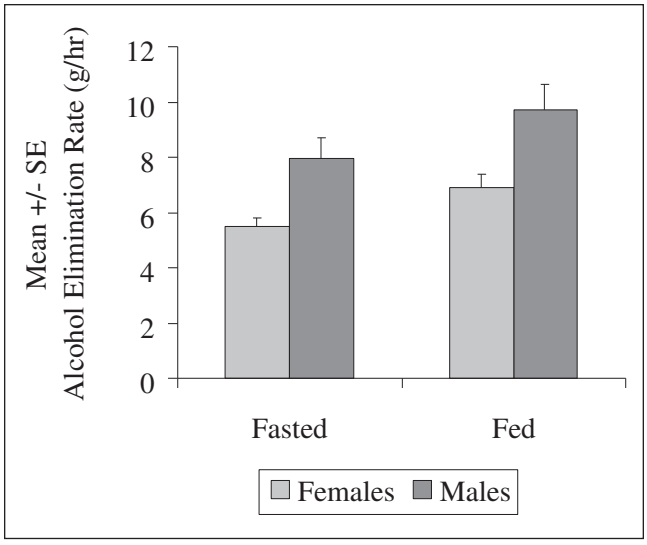

Figure 1. Mean ± SE alcohol elimination rates for female and male subjects during the fasted and fed sessions in Study I. There was a significant effect of gender (p = 0.009) and of session (p = 0.001).

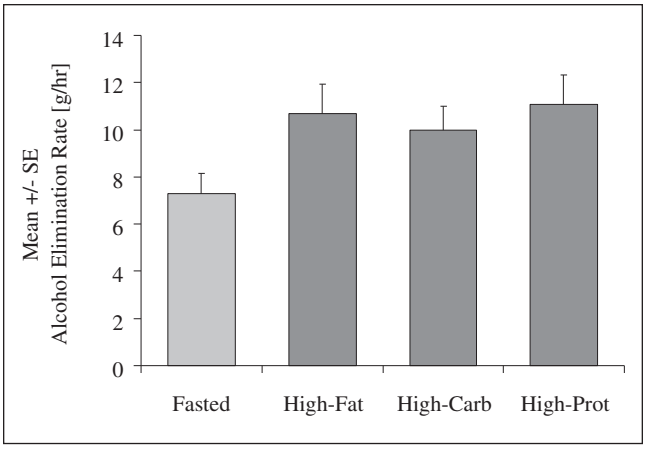

Figure 2. Mean ± SE alcohol elimination rates for subjects for each of the four sessions in Study II. All three fed sessions were significantly different from the fasted session (p = 0.001).

Figure 2 shows the mean alcohol elimination rates for each of the four sessions in Study II. Results showed a significant difference between the fasted session and the three "fed" sessions but no significant differences among the three fed sessions. There was a significant 45% average increase in AER following consumption of the 550-calorie meal, regardless of meal composition, compared to that following an overnight fast (p = 0.001). There was a large variability in the food effect, with the percent change in AER ranging from 16% to 74% across subjects. The mean percent change in AER was similar for high-fat, high-carbohydrate, and high-protein containing meals. Also, the food effect was consistent within subjects (i.e., subjects showed similar increases in AER across the three fed sessions).

DISCUSSION

The findings of these two studies indicate that food intake results in an increase in AER, as measured by clamping at 50 mg%. The increase in AER following food intake was similar for men and women. Also, the increase in AER was similar for meals of different compositions compared to the fasted condition. Comparison of the results of the two studies indicated an apparent difference in the magnitude of the average percent increase in AER between the two studies (25% vs. 45%). However, a large degree of variability in the percent change in AER was also observed in both studies. The clamping procedures used in the two studies did use different routes of administration for alcohol loading (oral vs. intravenous), but this would not be expected to influence the estimation of AER, which is based on the steady-state alcohol infusion rate. In fact, there were 3 subjects who participated in both studies. The AERs estimated for these subjects under fasted and fed conditions were comparable irrespective of the method of clamping. This is illustrated in Figures 3 and 4, which show the BrAC versus time and the infusion rate versus time profiles for an individual subject in the first study using oral clamping (Figure 3) and corresponding profiles for the same subject in the second study using IV clamping (Figure 4). As expected, comparable estimates of AER, under the fasted (12.1 g/h with oral clamping vs. 11.2 g/h with IV clamping) and fed (15.5 g/h with oral clamping vs. 16.1 g/h with IV clamping) sessions were obtained for this subject as well as for the other 2 subjects who completed both studies.

Several studies have investigated the influence of food on alcohol pharmacokinetics. However, most studies have employed oral alcohol administration and thus cannot disentangle the influence of food on the absorption and bioavailability of alcohol to the influence of food on the metabolism of alcohol, per se.[1,3] Two relatively recent studies have focused on the investigation of food and food composition on the pharmacokinetics of intravenously administered alcohol. The first study used a "clamping" method to establish steady-state breath alcohol levels, then administered meals with high-fat, high-protein, and high-carbohydrate contents to look at the change in infusion rates needed to main-

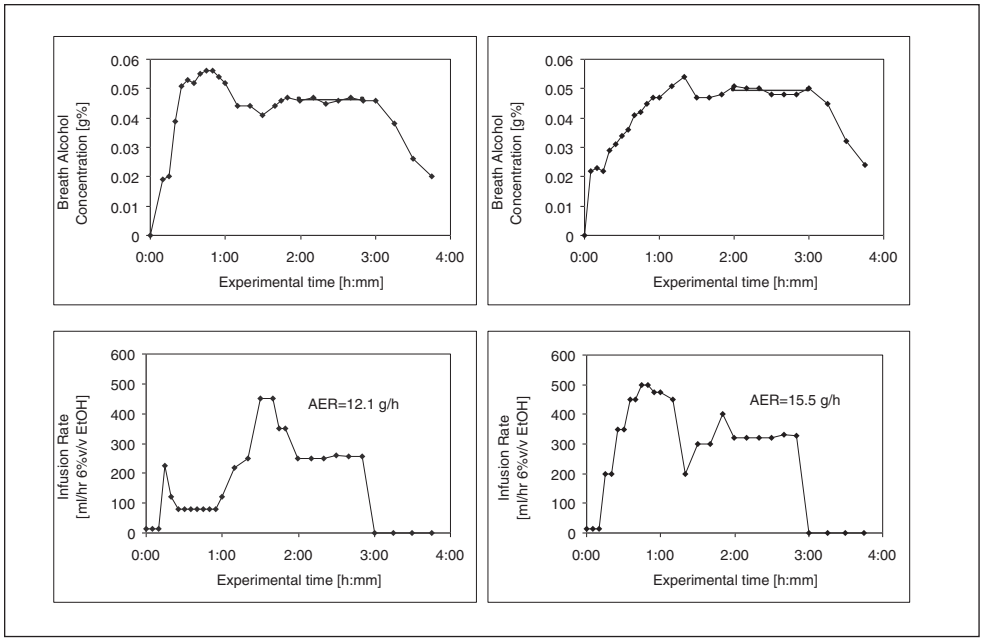

Figure 3. Breath alcohol concentration (BrAC) versus time and infusion rate versus time profiles for an individual subject, under fasted (left panel) and fed (right panel) conditions, in Study I.

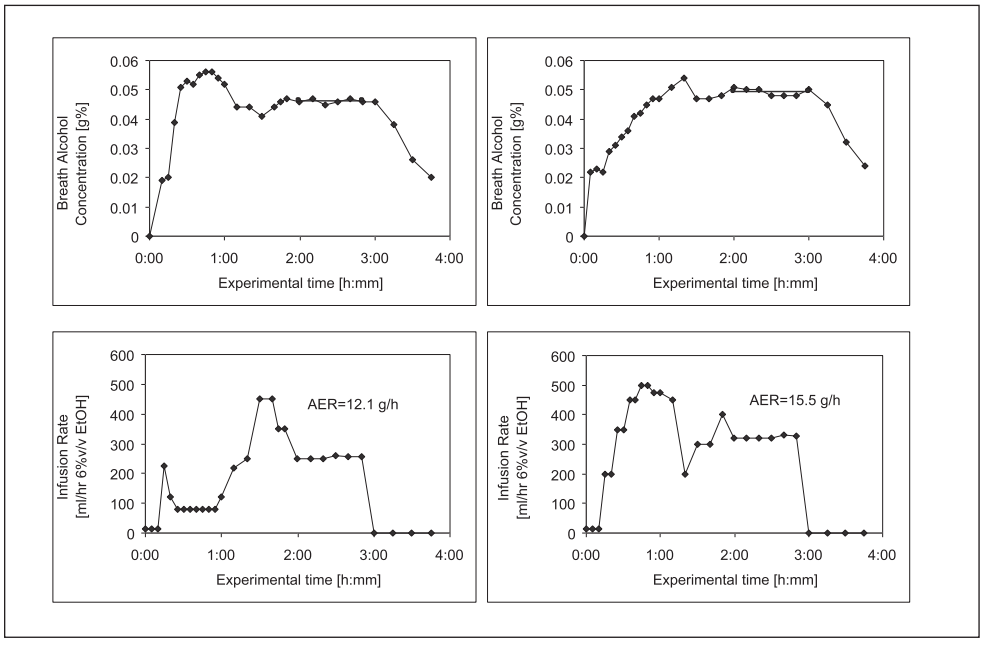

Figure 4. Breath alcohol concentration (BrAC) versus time and infusion rate versus time profiles for the same subject, under fasted (left panel) and fed (right panel) (high-protein) conditions, in Study II. The data from the high-protein meal condition are presented here for illustration, and similar profiles were obtained for the other fed conditions.

tain the same steady-state breath alcohol level.[2] The results of their study showed that the high-carbohydrate meal caused a significant increase in alcohol metabolic rate, while the high-fat and high-protein meals did not have a significant effect on the alcohol metabolic rate.

A more recent study by Jones et al[5] employed a single small dose of alcohol (0.3 g/kg body weight), administered as a short intravenous infusion within 15 minutes of consumption of a standardized breakfast containing different amounts of fat, protein, and carbo-

hydrates. The results indicated that peak blood alcohol levels and area under the BAC-time curve (AUC) were significantly lower after the meal compared to that following an overnight fast. Because of the low blood alcohol levels following the "fed" treatments, accurate estimates of disappearance rates could not be made for the different treatments. However, the time required to eliminate alcohol from the blood was shortened by 1 to 2 hours in the fed state. Importantly, there was no difference between the various meal types on their effect on the blood alcohol concentration-time curves.

The study by Jones et al,[5] as well as the results of the current study, indicate that the influence of food on the metabolism of alcohol does not appear to be due to any specific interaction with meal constituents. Probable mechanisms for the increased alcohol elimination include food-induced increases in the activity of alcohol-metabolizing enzymes, or rates of NADH reoxidation and/or increases in liver blood flow. Studies have shown that consumption of food does increase liver blood flow, as measured by indocyanine green clearance, and this increase in liver blood flow is sustained for up to 200 minutes following the meal.[12] Thus, food-induced increases in liver blood flow may be a potential mechanism to explain the nonspecific increase in alcohol elimination rates following the consumption of meals of differing compositions.

The primary objective of this study was to evaluate the influence of food intake on AERs using alcohol clamping. An increase in alcohol elimination rate following food intake would be expected to result in lower BrAC levels, as well as decreased intoxication and impairment following alcohol consumption. However, this could not be evaluated in our studies as the subjects were all clamped at the same BrAC level. Also, our clamping studies were performed at 50 mg%, which is a low to moderate BrAC level associated with social drinking. The percent increase in AER following food intake would be expected to be similar at higher BrAC levels, although this would have to be confirmed in future studies.

Although several factors can influence the rate and extent of absorption of alcohol, little data exist on factors that can acutely increase the rate of alcohol elimination. Increasing the rate of alcohol metabolism, especially following acute exposure, could be useful in reducing the duration of intoxication as well as the hazards associated with intoxication after drinking.[2]

We would like to acknowledge the excellent technical support of Deborah Sissons and Tishia James in the conduct of the studies, as well as the support of Laurie Hackward (GCRC bionutrition manager) and the dietetic and nursing staff of the GCRC.

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