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Alcohol Consumption and Alcohol Pharmacokinetics: Interactions Within the Normal Population

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We have analyzed the interrelationships between habitual alcohol consumption, peak blood alcohol concentration after a standard dose, and rate of alcohol metabolism in a group of 199 male and 213 female twins. Both peak concentration and rate of metabolism are strongly associated with alcohol consumption levels, even in the range of 0–10 g of alcohol/day. The peak concentration and rate of metabolism were strongly correlated in both men and women; this is not due to their common dependence on alcohol intake nor to experimental error. These results show that the threshold for effects of habitual consumption on alcohol pharmacokinetics is much lower than previously suspected, and that there are factors that reduce preabsorptive or first-pass metabolism but increase postabsorptive metabolism.

Key Words: Abstinence, Metabolic Rate, Peak BAC, Twins.

ALTHOUGH EFFECTS OF high habitual alcohol consumption on alcohol pharmacokinetics are well established, there appears to be little information on the possible effects of low to moderate consumption. The effects of alcohol intake on the rate of decrease of blood alcohol concentration (BAC) during the linear or near-linear elimination phase, and on the peak BAC after a standardized dose, have been studied in humans mainly by comparing subjects with alcohol dependence ("alcoholics"), with control subjects usually described as "social drinkers."[1–5] Such studies have generally been done with male subjects only.

We have evaluated the effects of habitual alcohol consumption in the range of 0–30 drinks/week on two pharmacokinetic variables: the peak BAC and the rate of decline in BAC, using data from a study of over 400 normal male and female twin subjects. Using twins as subjects allows a test of whether two correlated variables are each being affected by common genetic factors or common environmental factors. Under favorable circumstances, it may be possible to determine the direction of causation (whether A causes B, B causes A, or they are both caused by C), but this will usually require data from a very large number of twin pairs.[6]

In addition, analysis of results obtained from the same subjects on two occasions can determine whether correlations are due to short-term effects or errors affecting both variables, or to factors that are stable over time for each subject.

It has previously been noted[7] that significant correlations exist in this sample between the subjects' usual alcohol consumption and the rate of alcohol metabolism; and also that the peak and rate are positively correlated. This study examines these relationships in more detail.

SUBJECTS AND METHODS

The subjects for whom data were available were 199 men and 213 women aged between 18 and 35 years who took part in a study of genetic factors in alcohol metabolism and susceptibility to intoxication.[7] Of these subjects, 80 (36 female, 44 male) returned for repeat testing 4.5 months (average) after the first occasion.

Before taking alcohol, they had answered a questionnaire that included questions on habitual alcohol intake. A number of physiological and anthropometric measurements were made, including height, weight, and skin-fold thickness. They drank 0.75 g/kg of ethanol, diluted to 10% (v/v) in sugar-free, noncarbonated lemon cordial, over a period of 20 min. Blood samples were collected by finger-prick over the following 3 ½ hr and analyzed for alcohol by gas chromatography. The peak BAC and the rate of decrease in BAC were calculated for each subject. Details of the testing protocol and the methods are given in ref. 7. To avoid confusion, it should be noted that the current analysis of the data is based on the observed alcohol concentrations, not those predicted from the curve-fitting for each subject's data (which are also presented in ref. 7).

Estimates of BACs and the peak and rate of metabolism were independently determined from breath analysis and converted to blood alcohol equivalent using a blood/breath factor of 2100:1.

Ponderal index and a measure of adiposity were calculated from height and weight (height in mm divided by the cube root of weight in kg) and from skinfold thickness, respectively, and were log-transformed to produce a more normal distribution.

Subjects were grouped for ANOVA according to their declared usual weekly alcohol consumption as follows: group 0 = none, group I = 1–4 standard (10 g) drinks/week, group II = 5–10 drinks/week, group III = 11–30 drinks/week, and group IV = >30 drinks/week. The mean alcohol intakes of the subjects included in each group were 0, 2.5, 7.0, 18.6, and 42.8 drinks/week, respectively.

Statistical methods included correlation, and ANOVA without and with covariates, first of all separately for men and women and then, if no significant sex effects were shown on two-way ANOVA, using the results from both sexes. Log-transformation of the alcohol intake values was used for correlation analysis: to allow inclusion of the nondrinkers, the transformation used was $\log_{10}$ (number of drinks/week + 1). The

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measures of body composition (ponderal index and adiposity) were introduced as covariates to determine whether effects of alcohol consumption group were mediated by differences in body fat content. Basic statistics were performed with SPSS, and structural modeling was done with LISREL 7[8] using standard techniques.[9]

RESULTS

Peak BACs

The mean peak BACs by consumption category for the two sexes are shown in Fig. 1. ANOVA showed a significant effect of sex ($F_{1,402} = 25.48$, $p < 0.001$) so peak BAC data from male and female subjects were initially treated separately. There was no significant sex × alcohol consumption interaction affecting peak BAC. The two-way ANOVA showed a significant effect of consumption group ($F_{4,402} = 4.92$, $p < 0.01$), whereas one-way ANOVA with alcohol consumption group as the factor showed significant results in both men ($F_{4,194} = 3.15$, $p = 0.015$) and in women ($F_{4,208} = 2.68$, $p = 0.033$). To determine which contrasts between groups contribute most to the overall difference in means, t test comparisons between each possible pair of alcohol consumption groups were performed; the results (without correction for multiple comparisons) are given in Table 1.

Introduction of measures of obesity as covariates showed that, although body composition significantly affects peak BAC after a dose calculated from body weight, there were only negligible changes in the significance of the effect of alcohol consumption group.

Despite curvilinear relationships between consumption and peak concentration for the untransformed data, there was a significant correlation between log (weekly alcohol intake) and peak BAC both in men ($r = 0.16$, $p < 0.05$) and women ($r = 0.25$, $p < 0.001$).

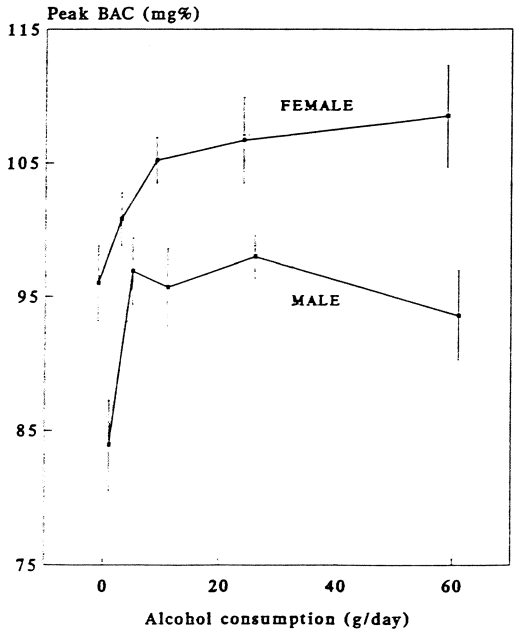

Fig. 1. Effect of alcohol consumption group on peak BAC after 0.75 g/kg of alcohol in 199 male and 213 female subjects (means ± SE).

Table 1. Significance of Differences in Peak BAC Between Alcohol Consumption Groups

Group	0	I	II	III	IV	
			Females			
0	—	NS	**	*	NS	(28)
I	**	—	NS	NS	NS	(68)
II	*	NS	—	NS	NS	(80)
III	***	NS	NS	—	NS	(31)
IV	*	NS	NS	NS	—	(6)
	(19)	(43)	(43)	(72)	(22)	
			Males			

Group 0, none; group I, 1–4 drinks/week; group II, 5–10 drinks/week; group III, 11–30 drinks/week; group IV, >30 drinks/week. Number of subjects in each group is shown in parentheses, and results for men and women are shown separately (men below and to the left of the diagonal, and women above and to the right). *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; NS (not significant), $p > 0.05$.

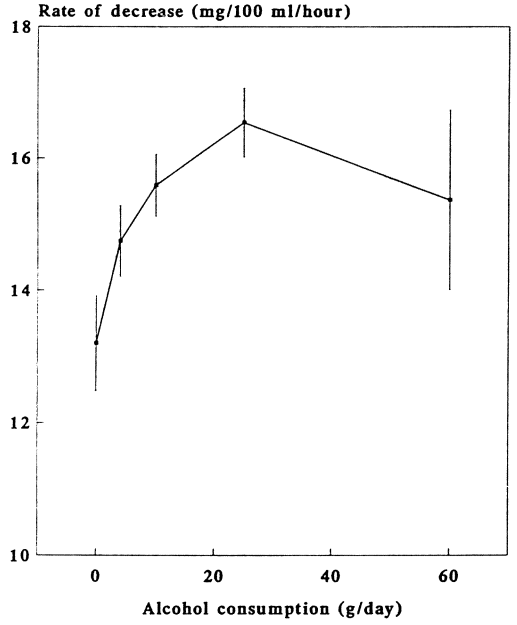

Fig. 2. Effect of alcohol consumption group on rate of decrease of BAC after 0.75 g/kg of alcohol in 412 subjects (means ± SE).

Rate of Decrease of BAC

For this variable, there was no significant difference between the sexes by ANOVA, and no sex × alcohol consumption interaction effect, so it was possible to pool the results for men and women without adjustment to a common mean. Significant differences were identified between the consumption groups ($F_{4,402} = 3.92$, $p < 0.01$). The effect of consumption on the rate of decline in BAC is shown in Fig. 2, with the contrasts between consumption groups summarized in Table 2. For the rate of decrease of BAC, there were significant correlations with log (weekly alcohol consumption) in both men ($r = 0.29$, $p < 0.001$) and women ($r = 0.20$, $p < 0.01$).

Association Between Peak BAC and Rate of Decline

The rate of decrease in BAC was strongly correlated with the observed peak BAC, both in men ($r = 0.576$, $p <$

Table 2. Significance of Differences in Rate of Decrease in BAC Between Alcohol Consumption Groups

	All Subjects				
Group	0	I	II	III	IV
0	—				
I	NS	—			
II	**	NS	—		
III	***	*	NS	—	
IV	NS	NS	NS	NS	—
	(47)	(111)	(123)	(103)	(28)

Group 0, none; group I, 1–4 drinks/week; group II, 5–10 drinks/week; group III, 11–30 drinks/week; group IV, >30 drinks/week. Number of subjects in each group is shown in parentheses. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; NS (not significant), $p > 0.05$.

Table 3. Genetic and Environmental Correlations Between Blood Readings of Peak BAC, Ethanol Elimination Rate, and Log Weekly Alcohol Consumption Based on 206 Pairs of MZ and DZ Twins

	Environmental		
	Peak	Rate	Consumption
Peak	—	0.60	0.07^{NS}
Rate	0.66	—	0.09^{NS}
Consumption	0.36	0.46	—
	Genetic		

Genetic correlations are shown below and to the left of the diagonal; environmental correlations are above and to the right. MZ, monozygotic; DZ, dizygotic; NS, not significant.

0.001) and in women ($r = 0.409$, $p < 0.001$). This correlation persisted when partial correlation, to control for possible effects of habitual alcohol consumption on both variables, was done: $r = 0.560$ for men and $r = 0.379$ for women, both $p < 0.001$.

The calculated slopes of the peak/rate regression were 0.179 in men and 0.129 in women, so that a change in peak concentration from 80 to 120 mg/100 ml would be predicted to lead to a change in rate of metabolism from 12.7 to 19.8 mg/100 ml/hr in men and from 12.9 to 18.1 mg/100 ml/hr in women; approximately a 50% increase in rate for a 50% increase in concentration. The regression slopes did not change significantly if nondrinkers were omitted from the calculation; 0.182 for men and 0.124 for women, or if only nondrinkers were considered; 0.103 for 19 men and 0.127 for 27 women.

Genetic and Environmental Correlation

To explore the causes of covariation between alcohol consumption and metabolism further, we performed a genetic analysis of the twin data for peak BAC and elimination rate, both measured in blood (as opposed to breath) samples, and log weekly alcohol consumption. We specified a saturated factor model (Cholesky decomposition) for both additive genetic and individual environmental sources of variance.[10] This was fitted to 6 × 6 matrices of the three measures for twin 1 and twin 2, for all five zygosity-sex twin groups. There was no significant heterogeneity between sexes in the fit of this model, and from the estimated factor loadings, the genetic and environmental correlations between the three measures can be calculated (Table 3).

There are significant genetic correlations of consumption with both peak (0.36) and rate (0.46), but the corresponding environmental correlations are both small and not significant.

There were also large correlations, both genetic (0.66) and environmental (0.60) between peak and rate. If genuine, such correlations would have important implications for our understanding of the pharmacokinetics of alcohol. However, it is possible that this correlation has arisen in whole or in part because the peak value may have been included in the calculation of the elimination rate. This would, of course, have the effect that any over- or underestimation of the peak value would cause an over- or underestimation of the rate of decrease. Because the rates were calculated some time ago[7] and the exact individual blood and breath sampling times are no longer available for any but the subsample of 80 individuals who returned for repeat testing, we are forced to test this possibility on the subsample; but the duplicate studies on these subjects also allow a cross-occasion comparison, which is instructive.

For the repeat subsample, we were able to calculate correlations of peaks with elimination rates estimated, including and excluding the peak datum. Correlations between peak and rate, when the latter is calculated excluding the peak datum, are only slightly lower (0.05–0.10) than when it is included.

The 8 × 8 correlation matrix for peak and rate (excluding the peak datum) measured in both breath and blood on two occasions are given in Table 4. To this matrix, we fitted the measurement model shown in Fig. 3, which uses all four measurements of peak (blood and breath, two occasions) as indicators of a latent peak variable, and similarly for rate. We are then interested in the correlation between the latent peak and latent rate variables from which the effects of measurement error have been removed, and this is estimated as 0.575, remarkably close to the genetic correlation of 0.66 estimated from the full data set of all 412 subjects. The model also allows for mode- (i.e., blood or breath) and occasion-specific correlations between peak and rate, and these are significant, although much smaller (0.11–0.23) than the underlying, measurement-error-free correlations.

DISCUSSION

Both the peak blood alcohol level attained after a standard dose of 0.75 g/kg and the rate of decrease of blood alcohol concentration were significantly associated with differences in levels of habitual alcohol intake, even within the normal or acceptable range. Indeed, the greatest differences were seen at the lowest level of alcohol use, between 0 and 10 g/day (see Figs. 1 and 2).

The significant effects of consumption group on peak BAC and rate of decrease persist, even if observations on pairs of twins are considered as not fully independent. The

Table 4. Correlations of Peak BAC and Elimination Rates Measured in Breath and Blood in 80 Individuals (36 Females, 44 Males) on Two Occasions, 4.5 Months Apart (on Average)

	Peak blood ethanol concentration				Rate of ethanol elimination			
	br1	bl1	br2	bl2	br1	bl1	br2	bl2
Peak br1	1.00							
Peak bl1	0.45	1.00						
Peak br2	0.32	0.58	1.00					
Peak bl2	0.43	0.63	0.66	1.00				
Rate br1	0.41	0.26	0.30	0.22	1.00			
Rate bl1	0.31	0.40	0.36	0.39	0.27	1.00		
Rate br2	0.21	0.19	0.50	0.35	0.49	0.37	1.00	
Rate bl2	0.13	0.18	0.32	0.45	0.32	0.31	0.48	1.00

Measurements are standardized separately for each sex. br, blood alcohol estimated by breath analysis; bl, measured blood alcohol concentration; 1, first occasion of testing; 2, second occasion of testing.

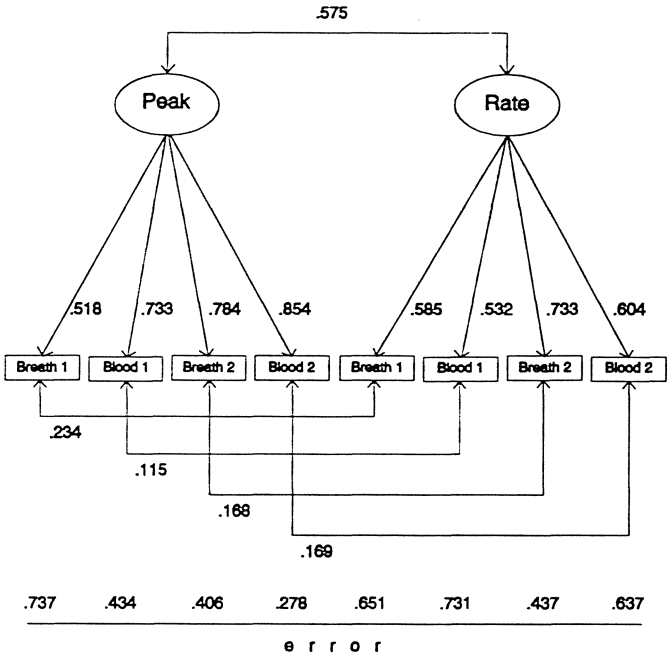

Fig. 3. Measurement model fitted by LISREL 7 to correlations of standardized peak BAC and elimination rates measured in breath and blood in 80 individuals on two occasions (Table 4). The correlation (0.575) between the latent peak and rate variables (in circles) represents the "true" correlation, with occasion and measurement specific effects removed. The loadings of each latent variable on its four measured indicator variables are shown and reflect the relative reliabilities of these measurements. There are also residual occasion- and mode-specific correlations between peak and rate. At the bottom of the figure are listed the residual error variances of each measurement. Fit of the model was χ^2 (15) = 14.88.

F-ratios are large enough to signify significance at the 0.01 level, even if the number of subjects was halved.

Peak Concentration

We found that the main contrasts, for both men and women, were between those who abstained from alcohol and those who did not (Table 1). For women, there were significant differences between abstainers (group 0) and groups II and III, who took between 5 and 30 standard drinks/week or ~10–40 g alcohol/day. For men, the abstainers showed significantly lower peak blood alcohol levels than all other groups, including subjects in group I who took only 1–4 drinks/week or <10 g/day.

Peak BACs after a dose of alcohol calculated from body weight will be affected by body composition, with people with more body fat reaching higher concentrations. This has often been cited as the reason for the difference in peak BAC between men and women. Our results show significant correlations between adiposity and peak BAC in both sexes, as expected, but correcting for this does not change the significant association between alcohol consumption and peak blood alcohol level. Therefore the association cannot be explained on the basis that people who drink more accumulate more body fat and therefore have a smaller volume of distribution/kg for the alcohol.

Renewed attention has been focused on the early part of the blood alcohol curve, because of the finding that higher BACs are attained after intravenous infusion of alcohol than after oral intake of an equal amount of alcohol. This difference is probably due to "first-pass metabolism" or preabsorption metabolism within the stomach.[11–14] Its degree has been reported to vary between men and women, and between alcoholics and controls. Preabsorption metabolism effectively reduces the dose of alcohol and will therefore be expected to reduce the peak BAC, the extrapolated concentration at time 0, and the area under the blood alcohol curve; and to increase the apparent volume of distribution of the alcohol.

The differences between people with different alcohol intakes may therefore be due to variation in gastric, preabsorption, metabolism of alcohol. Although it has been shown that alcoholics have less gastric metabolism of alcohol than control subjects, there appears to be no information about the effects of alcohol consumption at low levels on gastric alcohol metabolism.

Rate of Elimination

The rate of decline of BAC in these subjects increased with increasing habitual alcohol intake over the range from no alcohol (group 0) to 30 standard drinks/week (the upper limit of group III), which included 93% of the subjects studied. The mean value for group III was 25% above that for group 0. Above this level of alcohol consumption, there were too few subjects to be certain whether this trend continues, but the results shown in Fig. 2 suggest that it may not. Presumably, from the results published by other workers, there is then some further

threshold level of intake that results in a further increase in the rate of alcohol metabolism.

Effects of high alcohol intake on the rate of alcohol metabolism are well-known. However, the comparison groups in previous studies have generally been "alcoholics" and "controls," without regard to possible effects produced by alcohol consumption within the normal, nonhazardous range. This finding, that alcoholics eliminate alcohol faster than control subjects, is ascribed to the induction of a non-alcohol dehydrogenase pathway of alcohol metabolism.[15,16] Our data, being based on observation of the blood alcohol curves and confined to alcohol concentrations ~10–20 mM, cannot address the question of the mechanism of the effect. There might be some induction of microsomal alcohol metabolism, resulting in increased alcohol metabolism even at concentrations below the reported K_m for this system; or there might be an increase in liver size relative to total body mass, or some other unknown mechanism.

Genetic and Environmental Correlations of Peak, Rate, and Consumption

Analysis of the twin data has shown considerable genetic correlations of consumption with both peak and rate, but negligible environmental correlations. For the correlation between peak and rate, both genetic and environmental components were found.

We have investigated the substantial and unexpected correlation between peak and rate in a number of ways: by recalculation of the rate without inclusion of the peak value, by comparisons across occasions, and by estimation of genetic and environmental sources of the correlation. It is not an artifact of measurement, is stable over time, and is reflected in a high genetic correlation of these two aspects of metabolism. It is not due to a common dependence of peak and rate on consumption.

If peak and rate are indeed correlated because of a common underlying genetic variation between individuals (e.g., through a higher alcohol dehydrogenase activity in both the stomach and the liver), the positive correlation is unexpected, because this would lead to a greater early metabolism and thus a lower peak, a faster rate in the postabsorptive part of the blood alcohol curve, and a negative correlation.

Alternatively, an explanation for the peak/rate correlation might be found in the kinetic properties of alcohol-metabolizing enzymes; in general, a higher substrate concentration will lead to a greater rate of an enzymatic reaction. In this connection, it is interesting to consider the slope of the regression equation of rate on peak concentration. Class I alcohol dehydrogenases (which are generally considered the most important route of alcohol metabolism in normal subjects) have K_m values ~1 mM for ethanol,[17] and the peak alcohol concentrations in our subjects were ~20 mM. At such levels, a difference in substrate concentration should have negligible effects on the rate of reaction. From our results, a change from a peak concentration of 80–120 mg/100 ml (~16–24 mM) is predicted to give a 50% increase in rate, which is far too great for a low K_m reaction. Therefore any explanation of the correlation between peak and rate must lie elsewhere.

Direction of Causation Between Consumption and Peak or Rate

So far we have discussed the relationship between alcohol intake and peak BAC, or the rate of alcohol metabolism, on the assumption that differences in intake are the cause of differences in metabolism. However, a significant association or correlation could also be produced if subjects who metabolize alcohol more slowly are therefore likely to drink less. Similarly, it is conceivable that subjects who attain a higher peak concentration would obtain a greater reward from alcohol consumption and therefore be likely to drink more.

Because these subjects were all twins, in theory it is possible to consider the direction of causation in the association between these variables,[6,18] but this is difficult and beyond the scope of this study.

Rather, we are currently typing genetic polymorphisms of alcohol metabolizing enzymes in these subjects in the hope that these will provide the clue to the relationships between these variables. Extra information on the subjects' alcohol consumption at later times in their lives is also being collected, which may help to elucidate the direction of causation in the relationship between alcohol consumption and alcohol pharmacokinetics.

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