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LETTERS TO THE EDITOR

Alcohol Metabolism in Men and Women

A number of investigations of possible differences in alcohol metabolism between men and women have appeared recently, at least in part because of interest in the greater susceptibility of women to alcoholic liver disease.

In a recent issue of this Journal, Mishra et al.[1] reported a study of the effect of sex on the rate of decrease of blood alcohol, the volume of distribution, and the whole-body rate of alcohol metabolism, using pairs of male and female siblings to reduce genetic variability. They reported that alcohol elimination was faster in the female subjects than their male siblings.

This prompted us to re-examine data from a study of over 400 subjects[2] that included 194 men and 208 women. The subjects were twins, and 78 of them were members of dizygotic pairs of opposite sex. The results for men and women can therefore be compared both overall and by comparing the results of siblings of opposite sex.

Subjects ingested 0.75 g of ethanol per kilogram of body weight and blood samples were taken at intervals over the subsequent 4 to 6 hr; details are available in the published report. We have now calculated further pharmacokinetic variables and tested for sex differences in each. Results are presented as means and (in parentheses) standard errors (Table 1).

Taking the results for all subjects, the rate of decrease in blood alcohol in the postabsorption phase was essentially identical in these young adult men and women, but the women had a significantly higher peak blood alcohol. Consistent with these findings, the apparent volume of distribution of alcohol was greater in men. The sex differences in volume of distribution could not be accounted for by differences in body composition, estimated either as skin-fold thickness or ponderal index. Other pharmacokinetic parameters derived from these data showed that the estimated time for complete elimination of alcohol (ignoring the expected decline in rate at low concentrations) was less in men and the whole-body rate of alcohol metabolism was greater.

The results from the 39 pairs of opposite-sex twins are consistent with those from all subjects but the differences observed are generally smaller and of (at best) marginal statistical significance. Even though members of opposite-sex twin pairs of the same age were tested on the same day and would have shared many environmental influences, the use of sibling pairs does not add power (for these particular variables) when compared with the unpaired analysis on larger numbers of subjects.

Our results are consistent with the concept that first-pass alcohol metabolism is greater in men than in women, perhaps because of differences in gastric metabolism.[3] They are however at variance with the report of Mishra et al.[1] that alcohol metabolism (measured as the rate of decline of blood alcohol) is faster in women. Although Mishra et al. gave alcohol intravenously rather than orally, this would not be expected to increase alcohol metabolism preferentially in the female subjects.

Any differences in the rate of alcohol metabolism between men and women are small and unlikely to be of clinical significance. It is also worth noting that although first pass metabolism is probably greater in males, its

Table 1. Comparison of pharmacokinetic data for men and women after consumption of 0.75 g/kg of ethanol, orally. Values are given as mean and SEM, and comparisons are made both between all male and all female subjects and between male and female members of opposite-sex pairs only.

	All subjects (N = 402)			Opposite-sex twin pairs (39 pairs)			
	Males (194)	Females (208)	*p* (Unpaired *t* test)	Males	Females	Difference mean (SE)	(Paired *t* test)
Peak blood alcohol (mg/100 ml)	95.4 (1.14)	102.9 (1.10)	<0.001	95.3	99.8	4.51 (2.96)	0.136
Time to peak (min)	76.3 (1.90)	80.9 (1.87)	0.095	78.2	77.0	−1.13 (5.55)	0.833
Rate of decrease of blood alcohol (mg/100 ml/hr)	15.5 (0.5)	15.9 (0.50)	0.365	16.1	14.7	1.4 (0.9)	0.135
Extrapolated blood alcohol at time 0 (mg/100 ml)	115.0 (1.54)	124.2 (1.35)	<0.001	116.1	118.5	2.38 (3.22)	0.463
Extrapolated time to reach zero blood alcohol (min)	478.4 (9.5)	517.4 (13.7)	0.020	454.7	522.7	68.1 (32.9)	0.045
Apparent volume of distribution (liter/kg)	0.673 (0.009)	0.619 (0.007)	<0.001	0.661	0.648	−0.013 (0.020)	0.522
Whole body rate of alcohol metabolism (mg/kg/hr)	99.7 (1.58)	95.1 (1.76)	0.045	102.8	93.0	−9.75 (5.11)	0.064

relative importance decreases with increasing dose; after 0.75 g/kg the peak blood alcohol levels were only about 8% higher in the female subjects.

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Reply

The differences in results between the study of Whitfield et al. and our study are most likely due to the different routes of administration of ethanol. The oral administration of ethanol results in a much lower peak blood ethanol concentration than the intravenous administration. Higher blood ethanol concentrations in turn are associated with more rapid rates of ethanol elimination.[1] The peak ethanol concentration in females after the oral administration of 0.75 g ethanol per kg was 102.9 mg/dl in the study of Whitfield et al., which is much lower than the peak ethanol concentration of 139.9 mg/dl after the administration of the lower dose of 0.6 ethanol per kg intravenously in our study. Also peak ethanol concentrations were 18.6% higher in females than in males in our study as compared with a difference of only 7.3% in the study of Whitfield et al. The calculation of rate of ethanol elimination is obviously dependent on whether the data are analyzed by application of Michaelis-Menten kinetics or a zero-order model,[2,3] and the section of the curve chosen for analysis. Whitfield et al. refer for their methodology to a prior publication which unfortunately was not available at our Institution. Also of importance is that we studied females at a specified time in their menstrual cycle, while it is unclear whether Whitfield did likewise. In the study by Jones and Jones,[4] there was a trend for higher peak blood ethanol levels and rates of ethanol elimination from the beginning to the end of the menstrual cycle. Finally, we do not understand how the data of Whitfield et al. is consistent with the concept that first-pass alcohol metabolism is greater in men than women, since the higher peak ethanol concentrations in women as compared with men are most likely due to the lower volume of distribution of the ethanol in women.

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