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MATHEMATICAL MODELLING OF ETHANOL METABOLISM IN NORMAL SUBJECTS AND CHRONIC ALCOHOL MISUSERS

G. D. SMITH,* L. J. SHAW,† P. K. MAINI,† R. J. WARD,‡ T. J. PETERS‡ and J. D. MURRAY§

*Endocytosis Research Group, Clinical Research Centre, Watford Rd, Harrow, Middx, HA1 3UJ, U K.; †Centre for Mathematical Biology, Mathematical Institute, St Giles, Oxford, U.K.; ‡Dept Clinical Biochemistry, Kings College School of Medicine and Dentistry, Bessemer Rd, London, U.K.; and §Applied Mathematics Dept, FS-20, University of Washington, Seattle, U.S A.

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Abstract — The time course of ethanol disappearance from the blood has been examined in normal males and females and in alcohol misusers. Blood alcohol estimations were made over a period of 3 hr, following an oral dose of ethanol (0.8 g/kg body weight) administered in the form of whisky. Attempts were made to fit the data to zero order, first order and mixed zero + first order kinetics. In the majority (75%) of normal females the blood ethanol concentration was still increasing at 30 min. This was only seen in 50% of normal males and in 50% of non-dependent alcohol misusers, but not in dependent alcohol misusers. In all of the normal females the disappearance of ethanol could be adequately described by zero order kinetics. However, in the normal male group only 20% could be described by zero order kinetics, 10% fitted first order kinetics and the remainder required a mixed model of zero + first order. The rate constant for the zero order component of the control male group was identical to zero order rate constant obtained for the female control group. In the female alcohol misuser group, 40% of the curves could not be described by zero order kinetics and fitted best to a mixed model. The zero order component of the entire group was significantly increased (by 35%) compared to that obtained for the female control group. In the male dependent and non-dependent alcohol misuser groups, all blood alcohol concentration curves fitted best to mixed zero and first order kinetics. However, no significant differences were noted in the values of the kinetic parameters when compared with the male control group. It is suggested that the zero order component of the blood alcohol concentration curves is due to the action of liver alcohol dehydrogenase and the first order component represents redistribution to the tissues. The presence or absence of a first order component is attributed to differences in absorption rates from the gut.

INTRODUCTION

The kinetics of ethanol metabolism in both normal and alcohol misusing men and women have been studied extensively (Arthur *et al.*, 1984; Wagner *et al.*, 1989; Pieters *et al.*, 1990) to ascertain, firstly, the differences that exist between the sexes in their response to alcohol and, secondly, to gain a greater understanding of the pathogenic effects of ethanol and its metabolites. The major part of ethanol (80%) is metabolised in the liver, initially to acetaldehyde, which is the more likely agent to initiate and potentiate cellular damage because of its high chemical reactivity (Sorell and Tuma, 1985; Peters and Ward, 1988) and then to acetate. Changes in the activities of either alcohol (ADH) or acetaldehyde (ALDH) metabolising enzymes involved in the oxidation of ethanol may therefore have effects on the clearance of alcohol from the blood. More than 20 ADH isoenzymes exist, although current data point to no significant *in vivo* difference in the rate of ethanol metabolism between normal and atypical ADH phenotypes (Bostron and Li, 1986) or genotypes (Couzigou *et al.*, 1990).

Oxidation of ethanol may also occur in the gastric mucosa, which contains ADH class 3 isoenzyme. This enzyme activity is claimed to

be substantially decreased in female subjects (Frezza *et al.*, 1990) and reputedly causes higher circulating blood alcohol levels in these subjects (Pikaar *et al.*, 1988; Frezza *et al.*, 1990). Other factors which may also be important in causing differences in metabolism between males and females include a faster elimination rate (Cole-Harding and Wilson, 1987), a smaller volume of distribution of ethanol because of a lower water content in the body of women than men (Marshall *et al.*, 1983), hormonal factors (Brick *et al.*, 1986) and the smaller liver size in female subjects (Leung *et al.*, 1986).

Enhanced elimination of ethanol has been reported in alcohol misusers (Lieber, 1988), although the biochemical basis for this is unclear. The induction of the microsomal P450 ethanol metabolising system (MEOS) in chronic ethanol consumption may be responsible for this increase. However, the contribution of the MEOS to overall ethanol metabolism is controversial (Holtzman *et al.*, 1985). An increase in mitochondrial redox transport has been suggested as an alternative mechanism (Jenkins and Peters, 1978).

The classical approach to the study of the kinetics of ethanol elimination has been to view it as a zero order process. However, a number of studies have shown that the elimination curves cannot always be described by zero order kinetics, and various models of increasing complexity have been applied (Holford, 1987).

In this study we have examined the variation of blood ethanol concentration with time, following an oral dose of ethanol in both normal males and females and in alcohol misusers. In view of the lack of a consensus as to an appropriate model for ethanol clearance, we have not assumed a particular physiological mechanism, but attempted to find the simplest mathematical description of the data. We have then compared the subject groups in terms of the best fit model and their resultant parameters. We then discuss the possible physiological mechanisms that underlie the observed differences and the relevance of the observations to the current system of 'back-tracking' of blood alcohol levels in the medicolegal situation.

PATIENTS AND METHODS

The normal group comprised Caucasian subjects aged between 21 and 60 years, 11 males and 9 females, who were social drinkers of alcohol (< 84 g/week and < 56 g/week, respectively). They showed normal liver function, as assessed by the activities of serum gamma glutamyl transferase, alkaline phosphatase and aspartate amino transferase and mean corpuscular volume (MCV) which were well within their appropriate reference ranges.

The alcohol misuser groups, aged between 21 and 70 years, 15 males and 5 females had been admitted as in-patients for clinical assessment of their alcohol problem and showed haematological and biochemical changes consistent with alcohol misuse, e.g. raised MCV and abnormal liver function tests. None had cirrhosis, alcoholic hepatitis or decompensated liver disease. There were no significant differences between the non-dependent and dependent alcohol misuser subgroups.

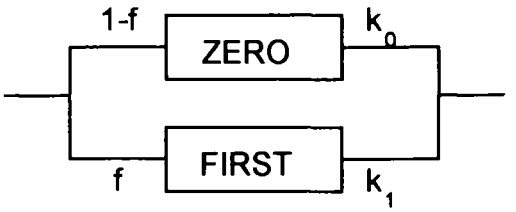
After an overnight fast, alcohol (Bell's whisky) was consumed over a period of 15 min (0.8 g ethanol/kg body weight). Venous blood specimens were collected into fluoride-oxalate tubes at 0 min and then at 30, 60, 90, 120, 150 and 180 min post-ingestion of alcohol, and the blood alcohol content was estimated enzymatically (Bucher and Redetski, 1951).

Using a severity of alcohol dependency questionnaire (Chick, 1980), the alcohol misusers were divided into non-dependents and dependents. Nine of the male alcoholic patients were designated as non-dependents while the remaining six patients were deemed to be alcohol dependent. Although the female alcoholic subjects comprised three dependents and two non-dependents, they were analysed as a single group in view of the small numbers.

The study was approved by the Harrow Health Authority Ethics Committee, and all subjects gave informed consent to the study.

Kinetic analysis and mathematical modelling

Initial kinetic analysis of the blood alcohol concentration curves was carried out by fitting to zero order, first order and a combination of zero and first order equations using non-linear regression analysis as depicted in Scheme 1.



Scheme 1. Diagrammatic representation of the model used to fit the observed data, where k_0 and k_1 are the zero order and first order constants, respectively. f represents the fraction of ethanol being eliminated by the first order process and has the value $1 \geq f \geq 0$. When $f = 0$ then all ethanol is cleared by the zero order process, and similarly when $f = 1$ all ethanol is cleared by the first order process. At intermediate values clearance is by a mixed model.

The model makes no allowance for the input of ethanol into the bloodstream. Therefore in a given set of data, if the value at the first sampling time (30 min) was lower than at the second (60 min), then the first time point was not included in the kinetic analysis. This can be justified from a consideration of the $t_{1/2}$ for absorption of alcohol from the gut. This has been estimated to be as small as 1.7 min (Wilkinson *et al.*, 1977), a value which should result in total absorption of the administered ethanol at 30 min post-ingestion. However, in a number of subjects in this study, absorption was still occurring at 30 min post-ingestion, suggesting a longer $t_{1/2}$ for absorption. In these cases, inspection of the data suggested a $t_{1/2}$ in the region of 10 min which would leave approx 5% of the alcohol dose to be absorbed at 30 min post-ingestion. However, even with a $t_{1/2}$ of 10 min, at 60 min post-ingestion only 0.6% of the administered dose is unabsorbed and thus absorption can be considered to be complete.

Goodness-of-fit was estimated from sign-tests and runs-tests of the residuals at best fit. The f-ratio test was used to indicate a significant improvement in the fit when choosing between models. Statistical comparison of the proportion of different groups bearing a certain characteristic was done using a chi-squared test with Yates' correction.

RESULTS AND DISCUSSION

Table 1 shows the haematological and biochemical parameters for the alcohol misuser patients subdivided into dependent and non-dependent alcohol misusers and compared with the controls. There was clearly little difference between the two groups of alcohol misusers in the extent of liver or marrow toxicity.

Comparison of male and female control groups

Figure 1 shows typical alcohol blood alcohol concentration curves for the male and female control subjects. Several trends can be discerned. In seven out of the nine female subjects a marked absorption phase was noted. That is, the maximum blood alcohol level was not found at the first sampling time point (30 min). This absorption phase was present in only five out of ten male subjects. This

Table 1. Haematological and biochemical parameters for the different subject groups

Patient group (n)	Chick scores	MCV (fl)	Serum GGT (IU/l)	Albumin (g/l)
Controls (10)	0–5	90.1 ± 2.1	28 6 ± 16.0	42 9 ± 3.9
Non-dependent misusers (8)	6–10	96.0 ± 8.2	96.2 ± 134	38 7 ± 5.8
Dependent misusers (8)	11–30	98.0 ± 6.6	136 ± 131	43.5 ± 4.5
Reference range	—	88–92	20–50	30–50

Values are expressed as mean ± SD.

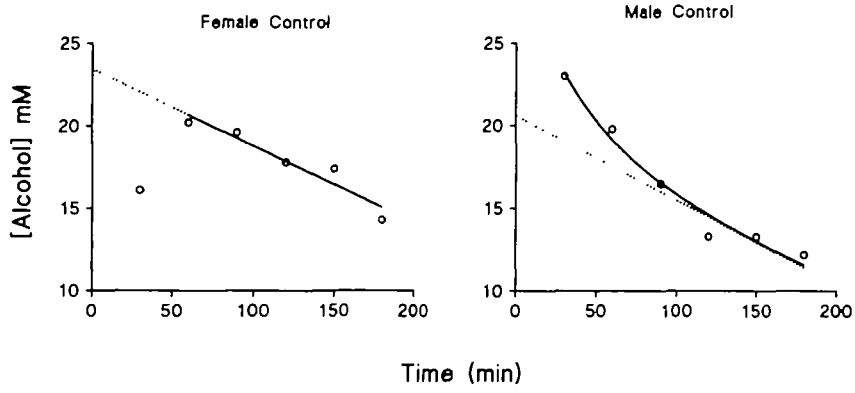


Fig. 1. Comparison of blood alcohol concentration curves in the male and female control groups. The figure shows representative curves from the two groups chosen because their individual fitted parameters were close to the mean values obtained for the groups as a whole. The dotted line represents the extrapolation of the zero order component to time = 0 min.

apparent difference in response does not quite reach statistical significance when comparing proportions ($P = 0.11$). As described in the Methods section, in the subsequent kinetic analyses the first time point was not included in the analysis if the time course showed an absorption phase. Table 2 summarises the values obtained for the various kinetic parameters in the different subject groups as discussed below.

Analysis of the time courses by zero order kinetics showed that all the curves of the female subjects could be adequately described by zero order. However, in the male control group, only 2 out of 10 could be adequately described by zero order kinetics. This difference was highly significant when comparing proportions ($P < 0.0002$). In one further case, the blood alcohol concentration curve showed a good fit to first order kinetics, but with the remaining seven subjects there was still systematic deviation of the points about the fitted

Table 2. Kinetic constants for the blood alcohol clearance curves

	t_0 (mM)	VD (l)	k_0 ($mM^{-1}min^{-1}$)	Decline in BAC (mg dl^{-1} hr^{-1})	k_1 (min^{-1})
Males					
Controls	24.2 ± 3.6	50.2	0.049 ± 0.008	13.5	0.049 ± 0.016
Non-dependent misusers	25.1 ± 3.8	48.5	0.053 ± 0.016	14.6	0.047 ± 0.012
Dependent misusers	22.8 ± 2.1	53.4	0.051 ± 0.019	14.1	0.061 ± 0.025
Females					
Control	24.9 ± 2.8	48.9	0.058 ± 0.011	16.0	N/A
Misusers	25.4 ± 2.2	47.9	0.078 ± 0.013	21.5	N/A

The table shows the values (mean ± SD) for t_0, obtained by extrapolation of the zero order component to zero time; k_0, the rate constant for the zero order component; k_1, the first order component where this is appropriate. The volume of distribution (VD) is obtained from t_0, assuming a 56 g dose of ethanol. The rate of decline in blood alcohol concentration (BAC) is obtained directly from the zero order rate constant.

line. The shape of the curve suggested that this might fit to a combination of zero and first order kinetics and the data were accordingly fitted to this model, with a significant improvement in fit. The mean value for the rate constant of the first order component (k_1) was 0.049 ± 0.016 min^{-1} (mean ± SD), which gives a $t_{1/2}$ = 14 min. The zero order component of the model had a rate constant (k_0) of 0.049 ± 0.008 mM^{-1} min^{-1}. This was not significantly different from the zero order rate constant for the female control group of 0.058 ± 0.011 mM^{-1} min^{-1}. If the zero order component of the male control group is extrapolated back to time = 0, a value of 24.2 ± 3.6 mM ethanol is obtained. This is indistinguishable from the value of 24.9 ± 2.8 mM obtained for the female group. This implies that there is a compartment for ethanol metabolism in both groups that has a maximum concentration of approximately 25 mM and is cleared by a process showing zero order kinetics with a $t_{1/2}$ = 223 min. In the majority of the male group a second compartment also plays a role in the disappearance of alcohol from the bloodstream. This does not appear to operate until higher blood alcohol concentrations are obtained and shows first order kinetics with a much more rapid rate of decline in alcohol concentration. Since the female control group shows evidence of slower absorption, this group may not reach a high enough blood alcohol level for the first order process to come into effect.

Comparison of female controls with female alcohol misusers

The blood alcohol concentration curves of two of the five alcoholic subjects showed no absorption phase and could not be adequately described by zero order kinetics. Like the majority of the male control group, these curves were best fitted by a combination of first + zero order kinetics. The mean value of the zero order component of all five subjects in the alcoholic group was significantly increased by 35% (0.078 ± 0.013 mM^{-1} min^{-1}; $P = 0.01$, *t*-test) when compared to the control group. This difference is illustrated in Fig. 2. There was no significant difference from controls in the value obtained by extrapolating back the zero order component to time = 0 (25.4 ± 2.2 mM ethanol). These results support the suggestion that a faster absorption phase results in a proportion of the alcohol entering a compartment from where its clearance is a first order process. The increase in the rate constant for the zero order process in the female alcoholics suggests an increase in the component responsible for the rate limiting step for the disappearance of alcohol from this compartment. Since there is no significant change in the starting concentration associated with this compartment then the $t_{1/2}$ for alcohol disappearance falls from 223 min to 160 min for the alcoholic group.

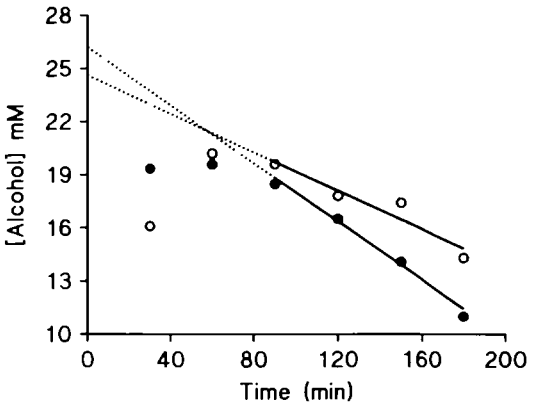


Fig. 2. Comparison of blood alcohol concentration curves in female control and female alcohol misusers. The figure shows representative curves from the female control (open circles) and female alcohol misuser (closed circles) chosen because their individual fitted parameters were close to the mean values obtained for the groups as a whole. The lines represent the best fit to zero order kinetics for the last four points in each curve.

Comparison of male controls with male alcohol misusers

The male misuser group was divided into two groups comprising non-dependent alcohol misusers and alcohol dependents as previously described. As was found with the male control group, 50% of the subjects in the non-dependent misuser group were still in an absorption phase at the first time point of the blood alcohol concentration curve. However, in the dependent group, no subjects showed an

absorption phase at 30 min. This difference in proportion was statistically significant when compared with either the control group or the misuser group ($P < 0.02$). All subjects in both the alcoholic groups showed an improved fit of the data to a combined first and zero order clearance curve. Unlike the case with the female alcoholics, there was no significant difference in the rate constant for the zero order component or the time = 0 value when comparing either group with the controls (non-dependents: $k = 0.053 \pm 0.016$ mM^{-1} min^{-1}, $t_0 = 25.1 \pm 3.8$ mM; dependents: $k = 0.051 \pm 0.019$ mM^{-1} min^{-1}, $t_0 = 22.8 \pm 2.1$ mM). There was no change in the value of the rate constant for the first order component of the clearance curves in the non-dependent group ($k_1 = 0.047 \pm 0.012$ min^{-1}). Although there is an apparent 30% increase in k_1 in the dependent group ($k_1 = 0.061 \pm 0.025$ min^{-1}), this difference does not reach statistical significance. Figure 3 demonstrates the overall similarity in the characteristics of blood alcohol disappearance in the male control and dependent misuser groups. Thus the most significant difference appears to be that in the dependents group, by the time the first sample is taken (30 min), the absorption phase is over, i.e. the dependents absorb ethanol into the bloodstream more rapidly. Although this would indicate higher initial blood alcohol concentrations, clearance at higher levels is by a first order process which remains constant irrespective of the subject group. Thus regardless of the maximal blood concentration reached, the $t_{1/2}$ for the decline down to the 25 mM level remains constant at approximately 14 min.

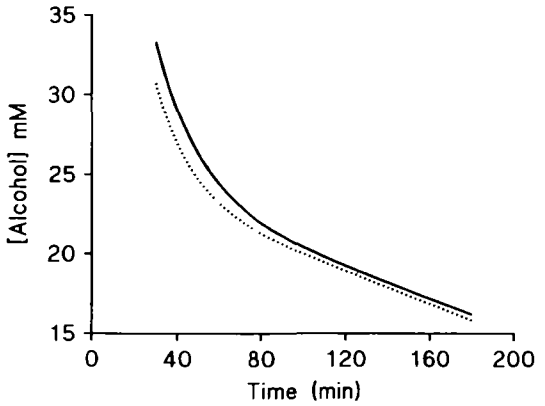


Fig. 3. Comparison of computed blood alcohol concentration curves for the male control and male dependent alcohol misuser groups.
The graph shows computed blood alcohol concentration curves for the control (solid line) and dependent (dotted line) groups calculated from the means of the parameters obtained for each group when fitting to a combination of first and zero order kinetics. The time course was computed from 30 to 180 min, but no attempt has been made to model the absorption component.

Physiological basis of the formal model

The data appear to indicate that there are two separate mechanisms for blood alcohol clearance, one of which only becomes effectively operative at high blood alcohol concentrations. A first order elimination of ethanol has been previously described (Hammond *et al.*, 1973; O'Neil *et al.*, 1984) at high blood alcohol concentrations, although the half-life of 4 hr for these observations is considerably greater than that observed here (14 min). A possible explanation for two separate elimination processes lies in the presence of two separate enzymic systems for the oxidation of ethanol. In the case of the liver, although alcohol dehydrogenase plays the major role in the preliminary metabolism of ethanol, the microsomal cytochrome P450 system (MEOS) can also oxidise ethanol. The K_m for ADH = 0.94 mM, which means that at alcohol concentrations above 10 mM the enzyme will be working under V_{max} conditions and thus show apparent zero order kinetics. The MEOS has a much higher K_m and providing the ethanol concentration stays below the K_m it will produce apparent first order kinetics for alcohol disappearance.

In order to test this hypothesis the data were modelled according to the following scheme:

$$\frac{d[A]}{dt} = -\frac{V_m\text{adh}\cdot[A]}{K_m\text{adh} + [A]} - \frac{V_m\text{meos}\cdot[A]}{K_m\text{meos} + [A]}$$

where $V_m$adh, $V_m$meos, $K_m$adh and $K_m$meos are the V_{max} and K_m for ADH and MEOS, respectively, and $[A]$ is blood alcohol concentration at time t.

However, the resulting kinetic parameters

were ill determined and indicated an estimated total MEOS activity that was so large that even at low ethanol concentrations it would completely dominate ethanol clearance. Furthermore, in order to obtain the observed first order kinetics the K_m for the MEOS would have to be in the order of 50–100 mM, which does not agree with literature estimates of 10 mM for the K_m for the MEOS (Keiding *et al.*, 1983). Thus it does not seem likely that the MEOS is responsible for the first order phase of alcohol removal from the bloodstream, or that it is playing a significant role in ethanol elimination in these studies. This conclusion has also been reached in ethanol elimination studies where administration was by intravenous infusion (Vestal *et al.*, 1977).

It is more likely that where seen, the first order disappearance is due to redistribution of the ethanol from the blood to peripheral tissues. The tissue distribution phase following intravenous ethanol administration (Vestal *et al.*, 1977) has been estimated to be up to 45 min. Thus it is possible that a tissue redistribution phase may be seen following oral ethanol intake, and that the extent of this phase would be affected by differences in stomach absorption kinetics. On this assumption, the observed zero order clearance represents metabolism of alcohol by ADH working under V_{max} conditions. The rates of decline in blood alcohol concentrations of the control groups (males 2.94 mM hr^{-1} 135 mg l^{-1} hr^{-1}; females 3.48 mM hr^{-1} 160 mg l^{-1} hr^{-1}) are a little lower than found in previous studies (180–202 mg l^{-1} hr^{-1}), where the investigators used oral administration of ethanol (Holford, 1987), but similar to that found by Jones and Neri (1985) who also used whisky as the source of ethanol (126 mg l^{-1} hr^{-1}). Extrapolation of the zero order rate to $t = 0$ gives a concentration of approx. 25 mM, which for a 70 kg body weight, the alcohol dose of 56 g gives a distribution volume of 48.7 l, again in good agreement with the studies of Jones and Neri (1985). The observation that zero order clearance in the female alcohol misuser group is significantly increased would suggest that the V_{max} for ADH is increased in this group. If increased ADH activity is not matched by increased aldehyde dehydrogenase activity then tissue damage due to increased concentrations of acetaldehyde may result and may account for the well known increased sensitivity of females to alcohol toxicity.

Calculations are sometimes made to estimate the blood ethanol concentration at some time prior to the actual time the blood sample was taken, the so-called 'back-tracking' procedure. The results presented here could have two different effects on this process. Since the female misuser group appears to metabolise ethanol some 30% faster than the control groups, then use of a standard rate based on control subjects would underestimate the back-tracked value. Secondly, given that a large number of subjects in various groups showed a first order phase to the disappearance of ethanol from the blood, then the timing of the blood sample with respect to the time of ethanol consumption becomes important. If the blood sample is taken within 1 hr ($4 \times t_{1/2}$ of redistribution) of the last drink, then extrapolation could result in too high a value. Within this time frame, blood alcohol levels may be dropping very fast and are not an accurate reflection of tissue levels.

In summary, we found little difference in the ability of normal males and females and of male alcohol misusers to metabolise ethanol. Approximately 50% of male controls and all male alcohol misusers showed a pronounced first order phase of alcohol disappearance which was attributed to tissue redistribution of ethanol. It is postulated that in the female control group, which did not show a first order phase, a slower absorption rate did not allow the maximum equilibrium concentration of ethanol to be exceeded. The female alcohol misusers showed increased metabolism of ethanol.

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