Michael C. Makoid *
James W. Sieg
Joseph R. Robinson ˣ
School of Pharmacy
University of Wisconsin
Madison, WI 53706

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* Present address: School of Pharmacy, University of Nebraska, Omaha, Neb.
ˣ To whom inquiries should be directed.

Elimination of Alcohol from Human Blood

Keyphrases □ Alcohol—kinetics of elimination from human blood, Michaelis–Menten equation □ Elimination kinetics—alcohol from human blood, Michaelis–Menten equation

To the Editor:

Traditionally, it has been assumed that the kinetics of elimination of alcohol from the blood of animals and humans can be described as zero order, *i.e.*, independent of the blood concentration (above about 2–3 m*M* or 0.09–0.14 mg/ml). Some investigators make this assumption simply because part of the alcohol concentration–time curve appears to be linear, while others believe that liver alcohol dehydrogenase is saturated at low concentrations of alcohol (1–5). Although some work (6–9) suggested non-zero-order elimination kinetics for alcohol in both animals and humans, the concept of zero-order kinetics persists (4, 5).

Newman *et al.* (6) gave various doses of alcohol to dogs, covering a wide range of concentration in blood, and found that there was a more rapid decrease in concentration at higher levels and doses than at the lower levels and doses. Eggleton (7) reported that Widmark's β value [the slope of the pseudolinear decline in blood alcohol concentration, expressed as milligrams of alcohol/(gram of blood × minutes)] in cats increased about 30% for every 1-mg/ml increase in alcohol concentration. If elimination kinetics were truly zero order, then the slope of the pseudolinear decline of blood alcohol concentration should be independent of dose or the C_0 value (the initial alcohol concentration at the beginning of the decline). Lundquist and Wolthers (8) showed that terminal serum alcohol concentrations in humans obeyed the integrated form of the Michaelis–Menten equation:

$$C_0 - C + K_m \ln C_0/C = V_m t \qquad \text{(Eq. 1)}$$

The corresponding Michaelis–Menten equation is:

$$-dC/dt = V_m C/(K_m + C) \qquad \text{(Eq. 2)}$$

In Eqs. 1 and 2, C_0 is the initial alcohol concentration, C is the alcohol concentration at time t, K_m is the Michaelis constant, V_m is the maximal velocity, and t is time. Studies in 10 normal subjects (8) gave an average K_m value of 2.03 m*M* (0.093 mg/ml) and an average V_m value of 0.22 mg of alcohol/ml of serum water/hr. Korsten *et al.* (10) reported a mean K_m value of 2.3 m*M* (0.11 mg/ml), estimated from terminal portions of alcohol disappearance curves derived from measurements of alcohol in whole blood from the arm veins of humans.

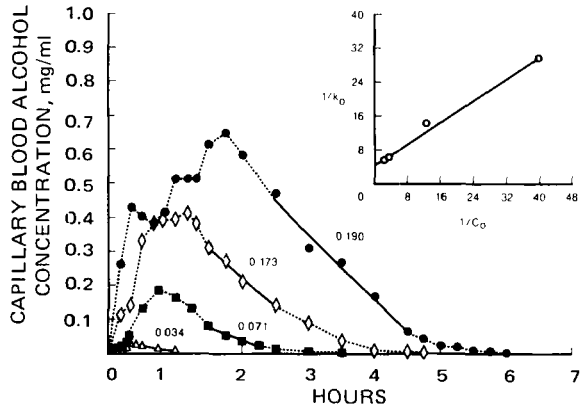

Figure 1—*Time courses of capillary blood alcohol concentrations in one of eight subjects following oral doses of 15, 30, 45, and 60 ml of 95% alcohol under fasting conditions. The absolute values of the slopes of the pseudolinear declines are shown above the declines (solid lines). Inset: double reciprocal plot of* $1/k_0$ *versus* $1/C_0$, *based on Eq. 3.*

As indicated previously, if elimination of alcohol from the blood of humans may be described by zero-order kinetics, then the absolute value of the slope of the linear decline of blood alcohol concentration, k_0, would be independent of dose or the C_0 value. If elimination kinetics are those of Michaelis and Menten, then the apparently linear segment of the alcohol concentration–time curve is actually slightly curved. Furthermore, evaluation as a linear component should disclose an increase in the absolute value of the slope with an increase in dose (or C_0) and a linear relationship between the reciprocal of the slope, $1/k_0$, and the reciprocal of the initial concentration, $1/C_0$ (11).

We followed the time course of alcohol concentrations in whole capillary blood of humans after administration of four different oral doses of alcohol in the fasting state. Capillary blood was used since: (*a*) the concentration of alcohol in capillary blood would be closer to the concentration in arterial blood than the concentration in venous blood, and the brain concentration would be determined by the concentration in arterial blood (12); (*b*) results with the Breathanalyzer are highly correlated with capillary blood alcohol concentrations (13); and (*c*) the large number of blood samples (20–40/subject/treatment) required to define adequately the entire time course makes use of capillary blood more desirable than venous blood, plasma, or serum. Alcohol was measured in 50-μl samples of capillary blood by a new head-space GLC method (14).

Eight normal male volunteers were given oral doses of 15, 30, 45, and 60 ml of 95% alcohol, made up to a volume of 150 ml with orange juice, in crossover fash-

ion, according to a Latin-square design. The subjects fasted overnight and for 3 hr after dosing. Blood sampling times were 0.067, 0.167, 0.333, 0.417, 0.5, 0.667, 0.833, 1, 1.167, 1.333, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.25, 6.5, 6.75, and 7 hr. Blood sampling started at 0.067 hr and ceased at 3 hr after the 15-ml dose, started at 0.067 hr and ceased at 4.75 hr after the 30-ml dose, started at 0.167 hr and ceased at 6 hr after the 45-ml dose, and started at 0.167 hr and ceased at 7 hr after the 60-ml dose.

The results obtained with a typical subject are shown in Fig. 1. Each k_0 value was estimated by the method of least squares from points that appeared to be randomly distributed about a straight line. In Fig. 1, the estimated values of k_0 are shown on the graph. The averages (and ranges) of the k_0 values for the eight subjects were: 15-ml dose, 0.074 (0.034–0.119); 30-ml dose, 0.121 (0.071–0.144); 45-ml dose, 0.137 (0.104–0.173); and 60-ml dose, 0.147 (0.135–0.562). Hence, the slope increased with an increase in dose. The data were also evaluated by means of:

$$1/k_0 = 1/(k_0)_{max} + \left[\frac{K}{(k_0)_{max}}\right]\left[\frac{1}{C_0}\right] \qquad \text{(Eq. 3)}$$

which is a linear transformation of:

$$k_0 = \frac{(k_0)_{max}C_0}{K + C_0} \qquad \text{(Eq. 4)}$$

In Eqs. 3 and 4, k_0 is the absolute value of the slope of the pseudolinear decline of capillary blood alcohol concentration; $(k_0)_{max}$ is the apparent value of k_0 for an infinite dose of alcohol and is analogous to, but not the same as, V_m; and K is analogous to, but not the same as, K_m (due to Eqs. 2 and 4 having the same form on the right-hand sides).

An example of the application of Eq. 3 is shown in the inset in Fig. 1. For this subject, a $(k_0)_{max}$ value of 0.232 mg/(ml × hr) and a K value of 0.148 mg/ml were calculated from the intercept, $1/(k_0)_{max}$, and the slope, $K/(k_0)_{max}$, of the linear regression line. For all eight subjects, the average value of $(k_0)_{max}$ was 0.163 mg/(ml × hr) with a range of 0.128–0.232. The average value of K was 0.073 mg/ml with a range of 0.046–0.148.

If average terminal capillary blood alcohol concentrations obey Eq. 1, and if V_m and K_m are reasonably constant from subject to subject, then it should be possible to fit all terminal data, obtained after several doses, simultaneously to a modification to Eq. 1:

$$C_0 - C + K_m \ln C_0/C = V_m(t - t_1) \qquad \text{(Eq. 5)}$$

where t_1 is a lag time and the other symbols have the same meanings as given previously. The lag time is the time required to adjust for the duration of the absorption–distribution phase of alcohol following a given dose. The terminal average blood alcohol concentrations of the eight subjects given four different doses of alcohol were simultaneously fitted to Eq. 5 using a computer[1] and the NONLIN program (15). Concentrations were weighted according to their reciprocals (*i.e.*, $1/C_i$) during the fitting. The lag time for the 30-ml dose was taken as 2 hr, and the lag times for the other three doses became parameters to be estimated as well as V_m, K_m, and C_0.

Figure 2 shows the results of the simultaneous fitting; the solid line drawn through the points is the model-predicted concentrations based on Eq. 5 and the least-squares estimates of the parameters. The time scales are staggered to take into account the least-squares estimates of the lag times. The values of the parameters estimated were: V_m = 0.290 mg/(ml × hr), K_m = 0.138 mg/ml, C_0 = 0.194 mg/ml, t_1 (60-ml dose) = 4.92 hr, t_1 (45-ml dose) = 3.70 hr, and t_1 (15-ml dose) = 0.112 hr. These values of V_m and K_m agree reasonably well with those estimated previously (8, 10). This fitting strongly supports the applicability of Eqs. 1 and 5 to alcohol blood concentration data[2].

The percent saturation of an enzyme system, if Eq. 2 applies, is given by:

$$\text{percent saturation} = 100(-dC/dt)/V_m = 100C/(K_m + C) \qquad \text{(Eq. 6)}$$

Use of the *in vivo* K_m value of 0.138 mg/ml estimated in the simultaneous fitting and of various values for C in Eq. 6 yields values of percent saturation of 42.0, 78.4, 87.9, 93.6, 94.7, and 97.8 for blood alcohol concentrations of 0.1, 0.5, 1, 2, 3, and 6 mg/ml, corresponding to 2.2, 11, 22, 44, 65, and 130 mM, respectively. Thus, it is obvious that the alcohol "enzyme system" is never "saturated," even at alcohol levels lethal to humans.

The apparent linearity of part of the downslope of the blood alcohol concentration–time curve is just a consequence of Michaelis–Menten kinetics (11). The shapes of the curves derived from Eqs. 1 and 5 are always pseudolinear for about two-thirds of the concentration range, independent of the initial value. The collapsing of Eq. 2 into:

$$-dC/dt = V_m \qquad \text{(Eq. 7)}$$

as the zero-order concept implies, is not justified with alcohol. This follows from the change in k_0 values with a change in dose as already illustrated. Such changes would not be predicted from Eq. 7.

The product of the V_m value of 0.232 mg/(ml × hr) and the average volume of distribution of 0.535 liter/kg (which we obtained by fitting blood alcohol con-

[1] IBM 370/168 digital computer.

[2] In the simultaneous fitting of average blood alcohol concentrations (Fig. 2), the sum of squared observations was 7.57×10^{-2}, the sum of weighted squared deviations was 4.03×10^{-3}, the coefficient of determination was 0.996, and the correlation coefficient for the linear regression of $\hat{C}$ on C was 0.998. The standard deviations of the estimated parameters were 3.9, 5.4, 2.2, 0.5, 0.7, and 16% of the estimated parameters for V_m, K_m, C_0, t_1 for the 60-ml dose, t_1 for the 45-ml dose, and t_1 for the 15-ml dose, respectively. Hence, the fit was excellent by several criteria.

In the fitting of blood alcohol concentration data obtained following oral administration, only terminal data should be utilized to estimate V_m and K_m of Eq. 5, as in Fig. 2, since earlier concentration data are a function not only of elimination but also of absorption and/or distribution. However, there is no reason to believe that the same *elimination* parameters do not apply at earlier times in the time course. Also, if the two-compartment open model with Michaelis–Menten elimination kinetics applies, rather than the one-compartment open model, then the V_m of the former model would be $(1 + k_{12}/k_{21})$ times the V_m value estimated from terminal data as in this paper; k_{12} and k_{21} are first-order distribution rate constants between the two compartments of the two-compartment open model.

The fitting of average blood alcohol concentrations, as in this paper, circumvents the problem presented previously (9), where variations in estimated parameters were obtained when individual data sets from the same subject were fitted. However, the fitting of the averages (Fig. 2) illustrates the applicability of Michaelis–Melten kinetics to data obtained following four different doses of alcohol.

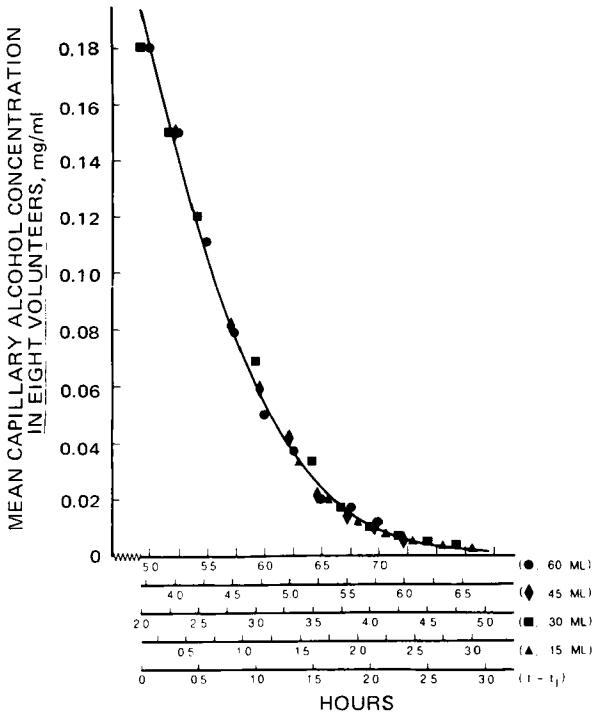

Figure 2—*Results of simultaneous nonlinear least-squares fitting to Eq. 5 of terminal average capillary blood alcohol concentrations of eight subjects given four different doses. The solid line gives the model-predicted concentrations.*

centration data obtained in six subjects given alcohol by constant-rate intravenous infusion) yields an estimate of 0.124 g of alcohol/kg/hr for the maximum elimination rate of alcohol in a normal male. For a 70-kg male, this is equivalent to 8.7 g of alcohol/hr.

In toxicology cases, where one wishes to estimate the future time course of blood alcohol concentrations, it is still valid to extrapolate an established pseudolinear decline in blood alcohol concentration down to about 0.2 mg/ml. However, this can only be done in individual patients who ingest a given dose of alcohol. It is invalid to predict the slope of the pseudolinear decline without a great deal of data and to compare slopes reported by two or more investigators who administer different doses of alcohol to different subjects. The slope of the pseudolinear decline is a function of C_0, V_m, and K_m, as indicated by Wagner (11) and the data in this report.

This work conclusively demonstrates that zero-order kinetics are inappropriate for describing the elimination of alcohol in humans. The slope of the pseudolinear decline should not be utilized as a measure of metabolism rate of alcohol as it has been used in the past (1, 2, 4–7). The rate of metabolism of alcohol is described more accurately by the V_m and K_m values and Eq. 2.

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John G. Wagner [x]
Paul K. Wilkinson
Allen J. Sedman
Donald R. Kay
Donald J. Weidler
College of Pharmacy and
Upjohn Center for Clinical Pharmacology
University of Michigan
Ann Arbor, MI 48104

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[x] To whom inquiries should be directed (at Upjohn Center for Clinical Pharmacology).

Analysis of Diffusion through Concentric Right Circular Cylinders and Concentric Spheres

Keyphrases □ Diffusion—concentric right circular cylinders and concentric spheres, models for drug release from tubular devices, cylindrical systems, and vaginal or GI lumen □ Drug release—tubular devices, cylindrical systems, and vaginal or GI lumen, concentric right circular cylinders and concentric spheres as models

To the Editor:

We recently have been modeling several diffusional systems involving diffusion through a series (two or more) of concentric right circular cylinders. The modeling encompasses (*a*) drug release from tubular devices, particularly in the presence of fluid boundary layers; (*b*) drug release from cylindrical systems containing drugs suspended in polymeric matrixes (1); (*c*) absorption of drugs from the vaginal lumen (2) or the lumen of the intestine (3), each of which, to a first approximation, may be considered a cylindrical membrane; and (*d*) combinations of *a*, *b*, and *c*.

A general phenomenon associated with all geometrical systems of this type, when diffusion is from the