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Pharmacokinetics of Ethanol After Oral Administration in the Fasting State[1]

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A nonlinear relationship between the total area under the blood ethanol concentration–time curve and the orally administered dose (mg/kg) of ethanol was observed in fasting subjects. A preliminary model, based on physiological considerations, was elaborated and shown, for the first time, to describe the entire time course of blood alcohol concentrations after four different doses of alcohol. The model could be refined by further experimentation.

KEY WORDS: nonlinear pharmacokinetics; Michaelis–Menten kinetics; gastric emptying rate; blood alcohol concentrations.

INTRODUCTION

Ethanol ingested on an empty stomach is very rapidly absorbed as it passes into the small intestine (1–3). When moderate amounts of ethyl alcohol are administered in solution, maximum blood alcohol concentrations are attained with stronger solutions. Very concentrated solutions are

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absorbed relatively slowly following oral ingestion because the high concentrations inhibit gastic peristalsis and cause pylorospasm (1,4), thus delaying the arrival of the alcohol in the small intestine. Large amounts of alcohol taken in dilute solution are also absorbed relatively slowly (1,5), possibly as a result of a volume effect on gastric emptying rate (6). Mellanby (5) reported different rates of absorption in man when equal amounts of alcohol were ingested in the form of whiskey (19% v/v) or stout (5% v/v). He also observed (7) that the absorption rate from 20% alcohol solution was less than 4 times faster than that of an equal volume of a 5% alcohol solution. He concluded that this result was produced by the inhibitory effect of the more concentrated solution on the stomach. Mitchell and Curzon (8) reported that "with higher concentrations, absorption is slowed due to slower evacuation from the stomach." Alcohol in solution has been shown to retard the gastric emptying rate in man (9), as measured by the increase in the volume of a test meal remaining in the stomach at a fixed time following the administration of solutions of increasing alcohol concentrations.

Numerous workers (2,10–24) have measured, either directly or via breath analysis, blood alcohol concentrations following oral administration of ethanol to man and small animals under both fasting and nonfasting conditions, and in conjunction with drugs which alter gastrointestinal motility. Most investigators (10–19) have not measured blood alcohol concentrations at early times; the first sampling time was usually $\frac{1}{2}$–1 hr after dosing. To accurately define the entire time course for pharmacokinetic purposes, early samples must be obtained as well as numerous samples at the tail end of the curve (22).

Traditionally, it has been assumed that the kinetics of elimination of ethanol from human blood can be described as zero order, i.e., independent of the blood concentration (above about 2–3 mM or 0.009–0.14 mg/ml). Although several studies (25–28) have indicated non-zero-order elimination kinetics, the former concept still persists (29,30). In a preliminary report of some of the data in this article, Wagner *et al.* (25) gave substantial evidence that the elimination of alcohol from human blood obeys Michaelis–Menten kinetics and not zero-order kinetics.

The study to be discussed was undertaken to (a) accurately define the entire time course of blood alcohol concentrations in fasting, adult, male volunteers; (b) determine the dose–response relationships for area under the curve and peak alcohol concentration; (c) determine the nature of the kinetics of absorption of ethanol in fasting subjects; and (d) elaborate a preliminary model for alcohol pharmacokinetics which could explain with reasonable accuracy the entire time course of blood alcohol concentrations after several doses.

Table I. Dosage Schedule and Treatments

Group	Subjects	Phase I	Phase II	Phase III	Phase IV
I	1, 2	A[a]	B	D	C
II	3, 4	B[b]	C	A	D
III	5, 6	C[c]	D	B	A
IV	7, 8	D[d]	A	C	D

[a] 15 ml of 95% ethanol diluted to 150 ml with orange juice.
[b] 30 ml of 95% ethanol diluted to 150 ml with orange juice.
[c] 45 ml of 95% ethanol diluted to 150 ml with orange juice.
[d] 60 ml of 95% ethanol diluted to 150 ml with orange juice.

EXPERIMENTAL

Protocol

Eight normal adult white male volunteers between the ages of 21 and 27 and weighing between 66 and 89 kg, with normal vital signs and laboratory screening values, were selected (see Table III). The study was performed using a latin square design with four groups of two subjects, arranged in order of increasing body weight. Each subject received 15, 30, 45, and 60 ml of 95% ethanol in orange juice (total volume of each dose was 150 ml) orally, at 1-week intervals according to the dosage schedule shown in Table I. The subjects fasted from 10 hr prior to dosing until 3 hr after administration of the alcohol. No alcoholic beverages (other than the prescribed alcohol) were consumed from 3 days preceding each phase of the study until the completion of that phase.

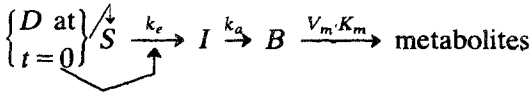
Just prior to dosing and at strategic sampling times following the 15, 30, 45, and 60 ml doses of 95% ethanol (by assay), 18, 25, 23, and 27 capillary blood samples, respectively, were collected. Each sample was collected from a fingertip, after lancing, in a 50-μl calibrated microsampling capillary tube. The blood samples were immediately mixed with an equal volume of internal standard solution, transferred to 6-ml amber glass serum vials (31), frozen, and kept in the frozen state until just prior to assay.

Analytical Method

Fifty-microliter capillary blood samples were assayed for ethyl alcohol according to the head-space gas chromatographic method of Wilkinson *et al.* (31). The analysis was performed on a Varian 2100 gas chromatograph equipped with flame ionization detectors.

Computer Analysis of Experimental Data

The average blood alcohol concentrations over the entire time course for all four doses were simultaneously fitted to the one-compartment open model with Michaelis–Menten elimination kinetics and input to blood subject to feedback regulation as shown in Scheme I. These data were fitted using the nonlinear least squares regression program, NONLIN (32), employing an IBM 370/168 digital computer.



Scheme I

In Scheme I, D represents the dose (grams of absolute alcohol initially placed in the stomach), S represents the amount of alcohol at time t that remains in the stomach, I represents the amount of alcohol at time t at the primary absorption site in the small intestine, B represents the amount of alcohol at time t in the blood and other fluids of distribution, k_e is the first-order rate constant for gastric emptying, k_a is the first-order rate constant for the absorption of alcohol from the small intestine, V_m is the maximum velocity [mg/(ml × hr)], and K_m is the Michaelis constant (mg/ml) for the elimination of alcohol from the body. B is assumed to be distributed in a volume, V. The assumed equation giving k_e and the differential equations corresponding to Scheme I, which were utilized in the simultaneous computer fitting, are as follows:

$$k_e = (k_e)_{\max}/(1 + aD^2) \tag{1}$$

$$dI/dt = k_e(FD/V)\, e^{-[k_e t]} - k_a I \tag{2}$$

$$dB/dt = k_a I - V_m B/(K_m + B) \tag{3}$$

In equation 2, F is the fraction of the dose which is absorbed and appears in the general circulation; this fraction is taken as unity (complete absorption and complete availability) for the 45 and 60 ml doses, but two parameters, $F_{15\,\mathrm{ml}}$ and $F_{30\,\mathrm{ml}}$, were estimated for the 15 and 30 ml doses of 95% ethanol, respectively.

In the fittings, the "I" and "B" were actually in concentration units, and were the respective amounts of alcohol divided by the volume, V. The "B" in equation 3 was the blood alcohol concentration in mg/ml. The doses, D, were 11.2, 22.4, 33.6, and 45.0 g of absolute alcohol, corresponding to doses of 15, 30, 45, and 60 ml of 95% alcohol, respectively.

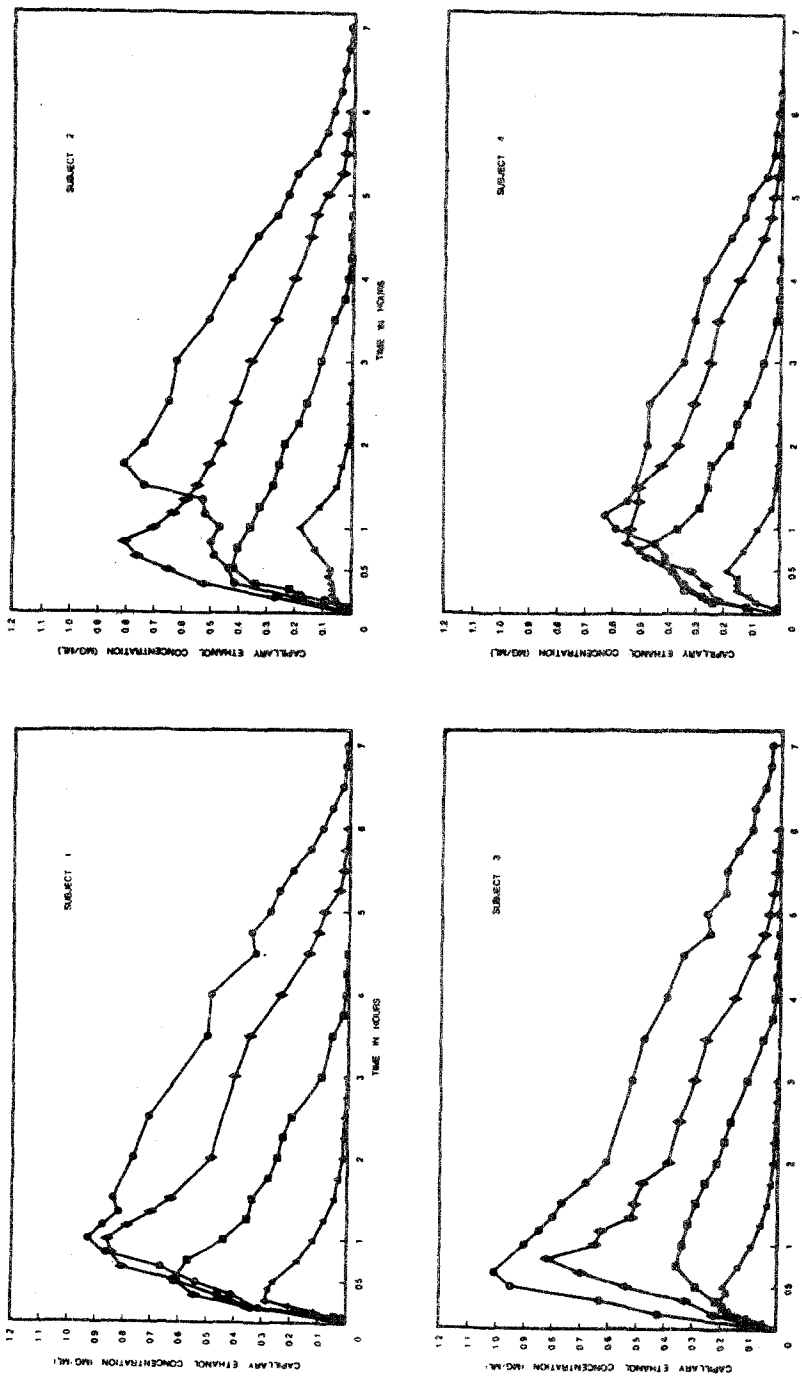


Fig. 1. Capillary ethanol concentrations measured following the oral administration of four different doses of ethanol to four adult male subjects 1, 2, 3, and 4. ▲ 15 ml, ■ 30 ml, ◆ 45 ml, and ● 60 ml of 95% ethanol diluted to 150 ml with orange juice.

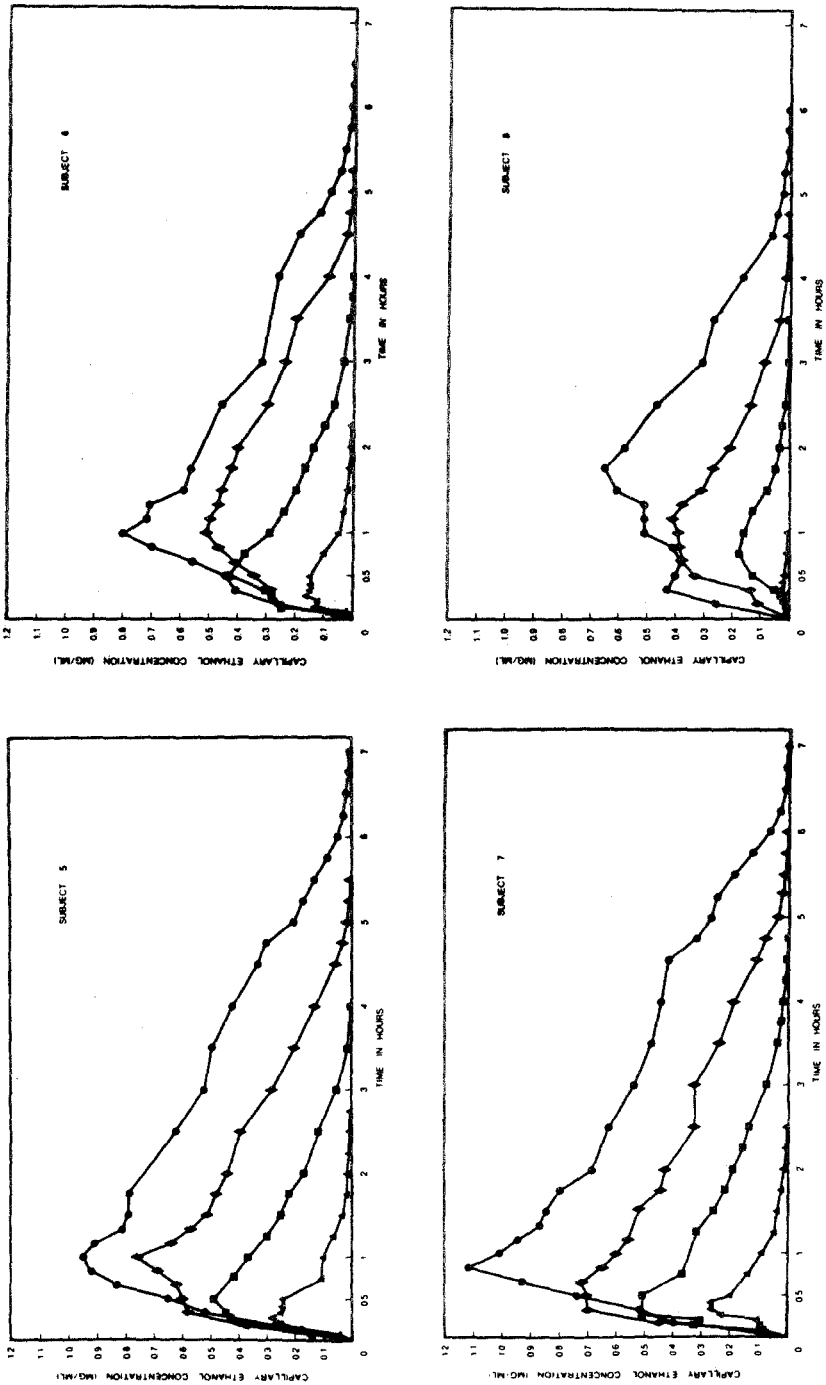


Fig. 2. Capillary ethanol concentrations measured following the oral administration of four different doses of ethanol to four adult male subjects 5, 6, 7, and 8. For key, see caption of Fig. 1.

RESULTS AND DISCUSSION

Figures 1 and 2 show the capillary ethanol concentration–time profiles for the eight subjects, while the mean capillary ethanol concentrations following the oral administration of the four different doses of ethanol are presented in Table II. These data were characterized by (a) a pseudolinear

Table II. Mean Fasting Capillary Ethanol Concentration (mg/ml) at Indicated Sampling Times Following the Oral Administration of Four Different Doses of Ethanol to Eight Adult Male Subjects

Time (hr)	Concentration (mg/ml) after 95% ethanol oral dose of			
	15 ml	30 ml	45 ml	60 ml
0.	0.	0.	0.	0.
0.067	0.032	0.071	—	—
0.133	0.096	0.019	—	—
0.167	—	—	0.28	0.30
0.2	0.13	0.25	—	—
0.267	0.17	0.30	—	—
0.333	0.16	0.31	0.42	0.46
0.417	0.17	—	—	—
0.5	0.16	0.41	0.51	0.59
0.667	—	—	0.61	0.66
0.75	0.12	0.40	—	—
0.833	—	—	0.65	0.71
1.0	0.090	0.33	0.63	0.77
1.167	—	—	0.59	0.75
1.25	0.062	0.29	—	—
1.33	—	—	0.53	0.70
1.5	0.033	0.24	0.50	0.71
1.75	0.020	0.22	0.43	0.72
2.0	0.012	0.18	0.40	0.64
2.25	0.0074	0.15	—	—
2.5	0.0052	0.12	0.32	0.57
2.75	0.0034	—	—	—
3.0	0.0024	0.069	0.28	0.45
3.5	—	0.034	0.22	0.43
3.75	—	0.017	—	—
4.0	—	0.010	0.15	0.36
4.25	—	0.0068	—	—
4.5	—	0.0052	0.081	0.27
4.75	—	0.0037	0.059	0.22
5.0	—	—	0.042	0.18
5.25	—	—	0.021	0.15
5.5	—	—	0.014	0.11
5.75	—	—	0.0099	0.079
6.0	—	—	0.0056	0.050
6.25	—	—	—	0.037
6.5	—	—	—	0.020
6.75	—	—	—	0.017
7.0	—	—	—	0.012

Table III. Vital Statistics of Subjects,[a] Doses, Areas Under the Concentration–Time Curves, and Peak Concentrations of Ethanol

Subject	Body weight (kg)	Height (cm)	Body surface area (m^2)	Age (yr)	Dose: ml of 95% alcohol	Dose: g of absolute alcohol/kg	Area[b] [(mg/ml) × hr]	Peak (mg/ml)
1	65.9	172	1.78	26	15	0.171	0.258	0.29
					30	0.341	1.017	0.62
					45	0.512	2.211	0.86
					60	0.683	3.198	0.93
2	70.5	178	1.87	23	15	0.160	0.169	0.18
					30	0.319	0.834	0.42
					45	0.479	1.996	0.81
					60	0.638	2.727	0.81
3	70.5	172	1.83	27	15	0.160	0.196	0.20
					30	0.319	0.778	0.36
					45	0.479	1.715	0.82
					60	0.638	3.089	1.01
4	71.4	178	1.89	23	15	0.158	0.147	0.19
					30	0.315	0.782	0.51
					45	0.473	1.437	0.55
					60	0.630	1.873	0.63
5	75.0	188	2.00	21	15	0.150	0.215	0.28
					30	0.300	0.781	0.49
					45	0.450	1.733	0.76
					60	0.600	2.968	0.95
6	75.0	178	1.92	23	15	0.150	0.130	0.16
					30	0.300	0.682	0.43
					45	0.450	1.322	0.51
					60	0.600	2.046	0.80
7	79.5	178	1.98	21	15	0.142	0.200	0.27
					30	0.283	0.836	0.51
					45	0.424	1.832	0.72
					60	0.566	3.249	1.12
8	88.6	179	2.07	21	15	0.127	0.011	0.025
					30	0.254	0.212	0.18
					45	0.382	0.775	0.41
					60	0.508	1.735	0.65

[a] All subjects were white and were either students or recent graduates. Only subject 7 was a smoker.

[b] The areas under the concentration–time curves were estimated with the trapezoidal rule.

phase, apparent after the peak concentration had been attained, which extended down to a blood ethanol concentration of about 0.20 mg/ml, followed by a portion, below 0.20 mg/ml, in which the concentration profiles tended to be curved with time, and (b) a nonlinear relationship between the area under the concentration–time curve and the oral dose (mg/kg) of ethanol administered.

Table III gives areas under the concentration–time curves, and Fig. 3 shows the area as a function of the administered dose (mg/kg) for all eight subjects. The upward curvature of the data in Fig. 3 is readily apparent, indicating a nonlinearity in the area–dose relationship. Theory requires that the data pass through the origin, i.e., zero area with zero dose. Any trend line drawn from the 0,0 point through the means or medians of the area distribution for each of the four doses (on a weight basis) would be curved and not a straight line.

From the data obtained in this study, the relationship between peak ethanol concentration and dose can be expressed as a linear function. Table

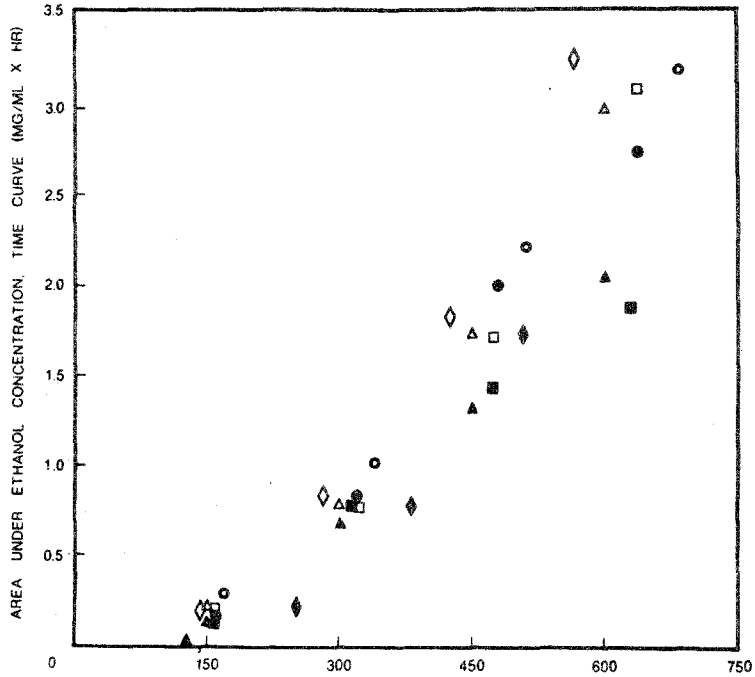


Fig. 3. Area under the ethanol concentration–time curve as a function of dose following the oral administration of four different doses of ethanol to eight adult male subjects. ○ Subject 1, ● subject 2, □ subject 3, ■ subject 4, △ subject 5, ▲ subject 6, ◇ subject 7, and ◆ subject 8.

Table IV. Parameters of the Least-Squares Linear Regression Lines[a] Relating Peak Alcohol Concentration (mg/ml) to Dose of Alcohol Expressed as Grams of Absolute Alcohol per Kilogram of Body Weight Following the Oral Administration of Ethanol to Eight Adult Male Subjects

Subject	Intercept (a)	Slope (b)		Slope of line forced through origin[c]
1	0.135	1.27	0.965	1.53
2	−0.015	1.43	0.949	1.15
3	−0.125	1.81	0.981	1.55
4	0.130	0.863	0.909	1.14
5	0.050	1.52	0.998	1.63
6	−0.25	1.33	0.980	1.28
7	−0.035	1.95	0.989	1.87
8	−0.210	1.66	0.995	1.11
Average	−0.012	1.48		1.41
C.V.(%)	—	23.1		19.8

[a] Peak = $a + b$ (dose).
[b] r is the correlation coefficient.
[c] Peak = (slope) (dose).

III gives the peak ethanol concentrations, and Table IV gives the parameters of the least-squares linear regressions of peak ethanol concentration on dose. Figure 4 shows the peak ethanol concentrations as a function of dose for all eight subjects.

The slope of the pseudolinear decline of blood ethanol concentrations has been shown to be dose dependent, such that the slope increases with increase in dose (25). Table V summarizes the initial alcohol concentration (C_0) used to estimate the slopes of the pseudolinear decline of capillary blood ethanol concentrations and the absolute values of the slope for all eight subjects. Wagner (33) has shown theoretically that evaluation of the apparently linear decline as a linear component yields an increase in absolute value of the slope with 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, $1/C_0$, when elimination kinetics are those of Michaelis and Menten (34). Wagner *et al.* (25) have shown that the average terminal blood alcohol concentrations following all four doses of ethanol can be fitted simultaneously to a modification of the integrated form of the Michaelis–Menten equation (28,34) shown as

$$C_0 - C + K_m \ln (C_0/C) = V_m(t - t_1) \tag{4}$$

where C_0 is the initial concentration, C is the concentration at time t, K_m is the Michaelis constant, V_m is the maximal velocity, and t_1 is a lag time to

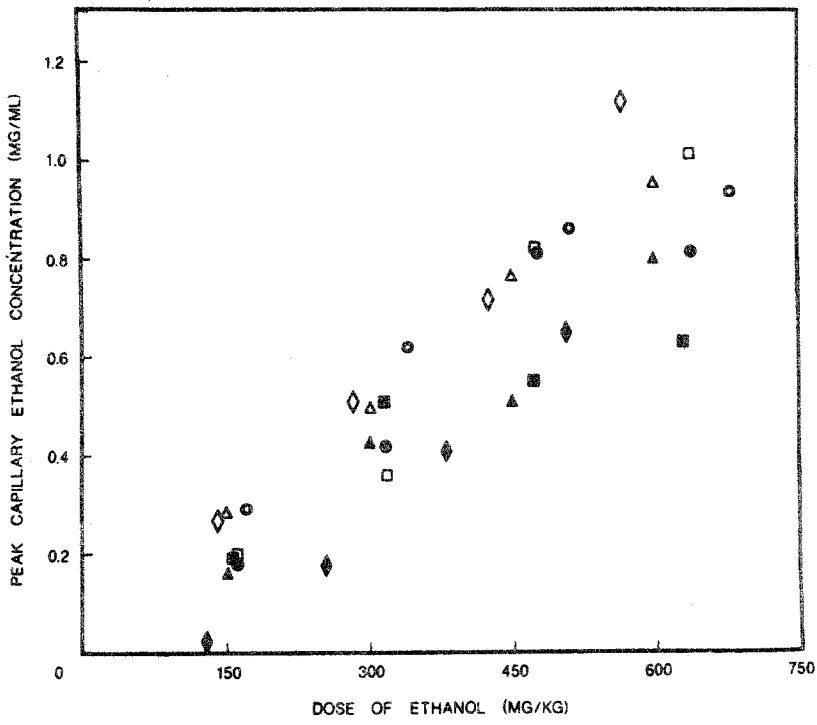


Fig. 4. Peak capillary ethanol concentration as a function of dose following the oral administration of four different doses of ethanol to eight adult male subjects. For key, see caption of Fig. 3.

Table V. Relationship of the Absolute Value of the Slope of the Apparently Linear Decline of Blood Alcohol Concentrations to Dose and Initial Blood Alcohol Concentration

Dose of 95% ethanol (ml)	Initial alcohol concentration[a] (mg/ml)		Absolute value of slope of apparent linear decline [mg/(ml × hr)]		
	Average	Range	Average	Range	C.V.(%)
15	0.065	0.025–0.12	0.074	0.034–0.119	44.1
30	0.26	0.078–0.36	0.121	0.071–0.144	19.0
45	0.43	0.31–0.51	0.137	0.104–0.173	16.6
60	0.63	0.47–0.78	0.147	0.135–0.562	19.3
			0.163[b]	0.128–0.232[b]	19.9

[a] The first alcohol concentration used to estimate the slope of the apparent linear decline of blood alcohol.

[b] The reciprocal of the intercept of a double reciprocal plot of $1/k_0$ vs. $1/C_0$ for the four points for each subject, where k_0 is the absolute value of the slope of the apparently linear decline and C_0 is the initial alcohol concentration.

adjust for the duration of the absorption–distribution phase following a given dose of ethanol.

To determine the nature of the absorption kinetics of ethanol in fasting subjects, the Wagner–Nelson method (35), modified for Michaelis–Menten elimination kinetics (36) (equation 5), was applied to the mean blood alcohol concentration data for all four doses:

$$A_T/V = C_T + \int_0^T V_m C/(K_m + C)\, dt \tag{5}$$

where A_T is the amount absorbed to some time T, V is the volume of distribution, C_T is the blood alcohol concentration at time T, and V_m and K_m are defined above; the maximum value of this function for each set of data is termed A_∞/V. The semilogarithmic plots of the amount not absorbed divided by the volume of distribution, $(A_\infty - A_T)/V$, vs. time are shown in Fig. 5. If the oral absorption of ethanol was a single first-order process, then all the semilogarithmic plots would be straight lines with the same slope,

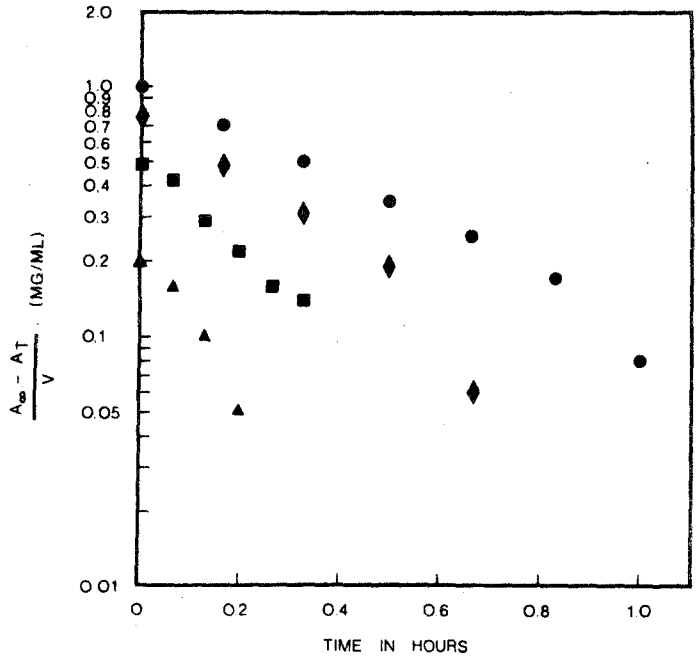


Fig. 5. Semilogarithmic plot of amount not absorbed divided by the volume of distribution as a function of time from mean blood alcohol concentrations following the oral administration of four different doses of ethanol to eight adult male subjects. For key, see caption of Fig. 1.

equal to the first-order absorption rate constant, k_a. As seen in Fig. 5, the trend of the points for each of the doses form a curved line on the semilogarithmic graph paper. Since the curves are not parallel, the absorption of ethanol in the fasting state appears to be nonlinear and dose dependent.

Ethanol has been shown to retard the gastric emptying rate, as indicated by the increase in residual test meals in the stomach after a set time with increasing alcohol concentration in the test meal (9). Therefore, it would seem reasonable to postulate some form of feedback mechanism which would alter the rate of transfer of alcohol from the stomach into the small intestine where most of the alcohol would be expected to be absorbed.

The model (Scheme I) is of the feedback type because of equation 1, which assumes that the rate constant for stomach emptying of the 150 ml total volume (alcohol plus orange juice) is dependent on the dose of alcohol administered and physiological considerations. Several studies (9,37,38) indicate that the osmoreceptors responsible for slowing of the gastric emptying rate are located in the duodenum. These receptors alter the gastric emptying rate in response to the osmotic pressure of fluids (which were previously gastric contents) in the lumen of the duodenum or small intestine (37). The inclusion of ethanol or many other solutes in a test meal will alter the gastric emptying rate (9). This alteration varies with the solute concerned. The $(k_e)_{max}$ in equation 1 is equivalent to the rate constant for gastric emptying of the 150 ml volume if no alcohol were present. Equation 1 indicates that the value of k_e will decrease as the dose of alcohol increases. An arrow from S to B, indicating that some of the alcohol is absorbed from the stomach directly, as some literature suggests, was not included in the model. Since only the B compartment was sampled, there was insufficient information to determine what fraction of the absorbed dose went directly from S to B and what fraction went from S via I to B.

The results of the simultaneous fitting of the average blood ethanol concentration over the entire time range are shown in Table VI and Fig. 6. From the data in this table, the doses of alcohol administered, and equation 1, the values of k_e calculated were 3.30, 1.09, 0.514, and 0.293 hr^{-1} for doses of 15, 30, 45, and 60 ml of 95% alcohol, respectively. The estimated value of k_a, 25.1 hr^{-1}, is very large compared with these rate constants for gastric emptying. Thus the results suggest that (a) once alcohol reaches the small intestine its absorption is extremely rapid, (b) observed blood levels of ethanol following oral administration are mainly controlled by gastric emptying rate and Michaelis–Menten elimination kinetics, and (c) there is essentially complete absorption and systemic availability of the entire dose of alcohol (since $F = 1$ for 45 and 60 ml doses and $F = 0.96$ for the 30 ml dose), except possibly at very low doses (since the estimated $F_{15\,ml} = 0.785$).

Table VI. Results of Simultaneous Fitting[a] of Average Blood Concentrations of Alcohol Over the Entire Time Range (Fasting Oral Study)

Parameter	Least-squares estimate	Standard deviation of the estimate
$(k_e)_{max}$ (hr^{-1})	10.2	1.49
a ($1/g^2$)	0.0167	0.000218
k_a (hr^{-1})	25.1	5.92
V (liters)	44.1	0.777
V_m mg/(ml × hr)	0.202	0.00657
K_m (mg/ml)	0.0818	0.00644
$F_{15\ ml}$	0.785	0.0238
$F_{30\ ml}$	0.960	0.0135

Measures of fit

		Dose of 95% alcohol (ml)			
	Overall	15	30	45	60
Sum 1[b]	10.1	0.164	0.993	3.19	5.71
Sum 2[c]	0.121	0.0254	0.0158	0.0439	0.0359
r^{2}[d]	0.996	0.986	0.996	0.995	0.998
Corr[e]	0.996	0.994	0.995	0.994	0.997
df[f]	82	10	14	15	19
N[g]	90	18	22	23	27

[a] Blood alcohol concentrations were weighted according to their reciprocals during the fitting.
[b] Sum 1 = the sum of squared observations.
[c] Sum 2 = the sum of weighted squared deviations.
[d] $r^2 = [\sum C^2 - \sum (\hat{C} - C)^2]/\sum C^2$, where $\hat{C}$ is the model-predicted ethanol concentration.
[e] Correlation coefficient for the regression of model-predicted vs. observed concentration.
[f] Degrees of freedom.
[g] Number of data points in the fitting.

Although the model employed does not take it into consideration, this apparent incomplete bioavailability at the lowest dose could have been caused by a "first-pass" phenomenon, which becomes saturated at relatively low doses of alcohol, but is unimportant at higher doses; however, the result could also have been caused by use of mean blood concentrations and inherent uncertainty of estimated parameters.

The estimated value of V (44.1 liters) in Table VI is 59.1% of the average body weight of the panel of subjects (74.6 kg) (see Table III). The average value of V, obtained by individual fitting of other subjects' pre- and postinfusion data to the one-compartment open model with zero-order input and Michaelis–Menten elimination, was 42.7 liters or 53.5% of body weight, but this panel of six subjects had an average body weight of 80.1 kg (39). Both these values agree with values given for total body water, the estimates of which are quite variable and depend on both age and body weight (40).

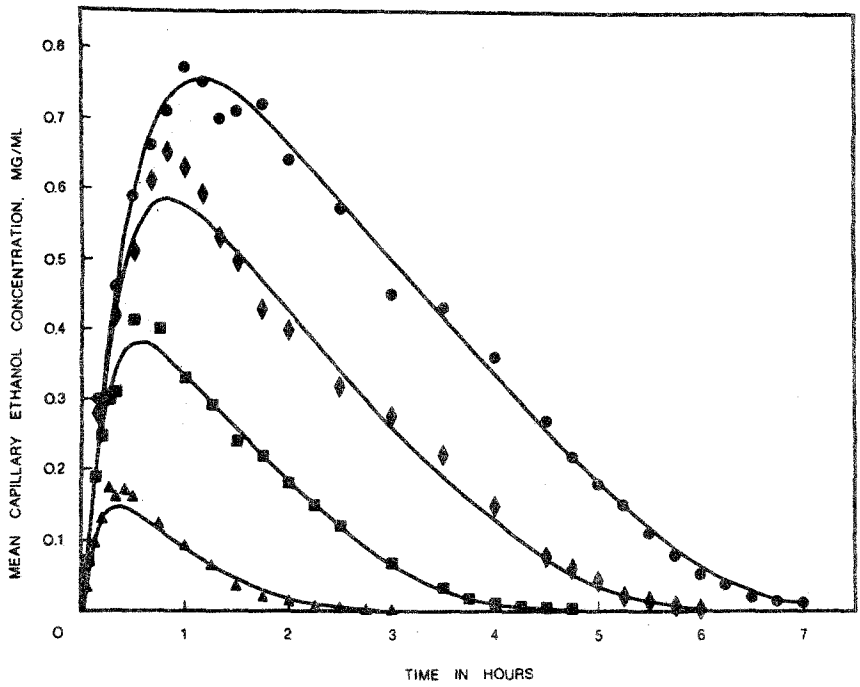


Fig. 6. Observed (points) vs. model-predicted (lines) mean capillary ethanol concentrations following the oral administration of four different doses of ethanol to eight adult male subjects. For key, see caption of Fig. 1.

The estimated value of V_m, 0.202 mg/(ml × hr), is very similar to the average value of 0.232 for the six other subjects given alcohol by constant-rate intravenous infusion. The estimated value of K_m, 0.0818 mg/ml, is almost identical to the average value of 0.0821 obtained in the same study (39).

Reevaluation of the data of Hunt and Macdonald (6) by regressing the half-life of gastric emptying of 39 pectin meals on the volume of the test meal gave an extrapolated estimate of 4.67 min for the half-life of gastric emptying of a meal of 150 ml volume, which was used in our study; the corresponding first-order rate constant (k_e) is 8.9 hr^{-1}. When the corresponding 39 k_e values of Hunt and Macdonald were evaluated by regressing ln k_e on ln V^*, where V^* is the volume of the test meal, the extrapolated estimate of k_e was 13 hr^{-1} for a V^* value of 150 ml. Therefore, these two values, 8.9 and 13 hr^{-1}, obtained by two different methods, for a 150 ml volume, bracket the value of 10.2 hr^{-1} for $(k_e)_{max}$, which would be the predicted gastric emptying rate constant for 150 ml of water containing no alcohol.

Thus the model (Scheme I) gave parameter estimates consistent with those obtained from intravenous infusion studies (29) and with data reported in the literature concerning the stomach emptying rate of liquid meals.

There are certain deficiencies in the preliminary model (Scheme I and equations 1–3). These are as follows: (a) Appreciable amounts of alcohol are absorbed from the human stomach (41), but the model ignores this. Without simultaneous sampling in compartments S and B of Scheme I, one could not accurately estimate the fractions of the absorbed dose involved in direct S to B and S via I to B pathways. (b) Small percentages (1–5%) of the alcohol in the body are excreted unchanged in the urine and via the lungs in the breath. The model ignores these routes of excretion. Without simultaneous sampling of urine, the breath and blood rate constants involved in these processes could not be estimated. Although Fig. 6 indicates that the model-predicted concentrations near the peak represent the observed data very well for the highest dose, they underestimate the observed data for the three lowest doses. (c) Although the one-compartment open model with Michaelis–Menten elimination kinetics reasonably well predicted alcohol blood concentrations both during and following constant-rate infusions of ethanol in six out of seven normal volunteers (39), there is also evidence of multicompartmental pharmacokinetics for ethanol in man in that the time courses of venous and capillary alcohol concentrations are different (42). (d) Equation 1, used to estimate the rate constant for stomach emptying of alcohol, k_e, from the dose of alcohol administered, is empirical. In future studies in man if isotopically labeled ethanol is utilized, if stomach emptying is monitored by external scanning, and if alcohol is estimated in urine, breath, and venous and arterial (or capillary) blood, then the resulting data will most probably allow considerable improvement on the preliminary model.

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