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Use of a Two-Compartment Model to Assess the Pharmacokinetics of Human Ethanol Metabolism

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The relationship between blood ethanol concentration and hepatic ethanol metabolism commonly is calculated using the Michaelis-Menten equation and a one-compartment model that assumes equality of blood and hepatic ethanol concentrations. However, at low blood concentrations, most of the ethanol arriving at the liver is metabolized, and hepatic ethanol concentrations may fall far below that of the entering blood. We have developed a two-compartment model of ethanol metabolism that accounts for the fall in ethanol concentration that may occur as blood traverses the liver and used this model to make predictions concerning ethanol metabolism at various blood ethanol concentrations. The two-compartment model predicts that near-complete saturation will occur more abruptly and at a lower blood concentration (~3 mM) than is the case with the one-compartment model. Thus, the two-compartment model predicts a near-constant ethanol elimination rate for blood ethanol concentrations above 3 mM (as commonly observed in human subjects), whereas the one-compartment model predicts an increasing elimination rate over the range of concentrations observed in experimental studies. In agreement with observed data, the two-compartment model predicts that first-pass metabolism should be extremely sensitive to the rate of ethanol absorption. Application of this model to previously published data indicated that, when absorption was slowed via concomitant food ingestion, first-pass metabolism accounts for ~50% and 10% of ethanol dosages of 0.15 g/kg and 0.3 g/kg, respectively. When ingested without food, there is negligible first-pass metabolism of even very small ethanol dosages (0.15 g/kg). These findings suggest that first-pass metabolism is an unimportant determinant of the blood ethanol response to ingestion of potentially inebriating doses of ethanol.

Key Words: Ethanol, Model, Blood Ethanol, Metabolism, First-Pass Metabolism.

UNDERSTANDING OF the relationship between the blood ethanol concentration and the rate of hepatic ethanol metabolism has both clinical and experimental value in that it allows prediction of ethanol metabolism at any blood ethanol concentration. As will be demonstrated, precise knowledge of the rate of metabolism at varying blood ethanol concentrations is particularly critical to accurate estimation of the quantity of alcohol removed by first-pass metabolism (FPM).

For a short period following cessation of input of ethanol into the circulation, the blood ethanol concentration declines rapidly as distribution in total body water is superimposed upon metabolism. After distribution, as illustrated by the data of Wilkinson et al.[1] in Fig. 1, blood ethanol concentration typically declines at a near-constant rate until the blood ethanol concentration reaches ~3 mM, at which point the rate of decline falls off in a roughly exponential fashion. This pattern of ethanol metabolism suggests that elimination follows Michaelis-Menten kinetics with saturation of metabolism occurring at blood concentrations >3 mM. Given these kinetics, the rate of ethanol metabolism at any moment may be predicted from the Michaelis-Menten equation:

$$\text{Rate of metabolism} = V_{max}[C_L/(C_L + K_m)] \qquad (1)$$

Because virtually all elimination of peripheral ethanol occurs in the liver, V_{max} is the maximal metabolic rate of the liver, K_m is the hepatic ethanol concentration that yields half-maximal elimination rate, and C_L is the ethanol concentration at the hepatocyte.

Most previous workers have treated the problem of relating the metabolic rate to the blood ethanol concentration as a simple matter of inserting the measured blood ethanol concentration, along with values for V_{max} and K_m, into the Michaelis-Menten equation. This treatment assumes that liver and body water are one well-mixed pool containing the same ethanol concentration. However, the concentration term in the Michaelis equation is *not* the blood ethanol concentration, but rather the ethanol concentration to which the hepatocyte is exposed. To the extent that these two concentrations are not identical, sizable errors could arise with the conventional single compartment model.

Table 1 shows that, when ethanol metabolism is calculated using typical V_{max} and K_m values[1] reported for the one-compartment model, major differences may exist between blood and hepatic ethanol concentrations. For example, at a 1 mM blood ethanol concentration, the one-compartment model predicts that hepatic metabolism would remove ~87% of the ethanol entering the liver. As a result, hepatic ethanol concentration would fall from 1 mM to 0.13 mM, a concentration that would yield a metabolic rate of only 0.26 mmol/min, as opposed to the 1.3 mmol/min rate predicted from the peripheral blood ethanol concentration. With a blood alcohol concentration of 0.5 mM, the one-compartment model predicts that the liver

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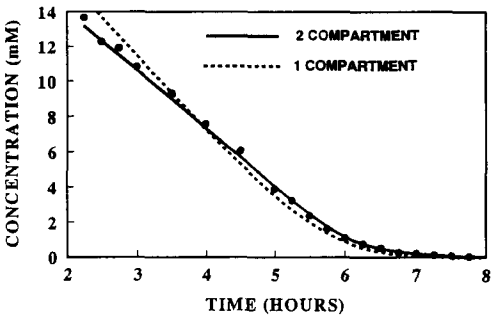

Fig. 1. Comparison of observed decline in blood ethanol concentration and the rates of decline predicted by the one-compartment and two-compartment models. The points (●) represent the average blood ethanol values observed by Wilkinson et al.[1] after cessation of a 2-hr constant infusion of ethanol in six male subjects. Data predicted for the one-compartment model (– – –) were determined from Eq. 1 in the text using a K_m of 1.8 mM and a V_{max} of 3.6 mmol/min (the kinetic constants that Wilkinson et al. calculated to provide the best fit to the observed data). Data for the two-compartment model (—) were calculated as described in the text.

would metabolize ethanol faster than it was being delivered!

As illustrated in Table 1, at low blood ethanol concentrations, the inappropriate assumption of equal blood and liver ethanol concentrations could result in relatively enormous overestimations of metabolic rate. In practice, these errors have been minimized by the selection of K_m and V_{max} values that provide the best fit to observed ethanol elimination curves. The best fit is provided by the use of artificially high K_m [i.e., an apparent K_m (K_{app})] and V_{max} values, although as demonstrated in Fig. 1, the fit of the predicted blood concentrations to the observed values remains imperfect.

It is our thesis that hepatic ethanol metabolism should be better predicted by a model that attempts to account for potential discrepancies between blood and hepatic ethanol concentrations. To this end, we have described a two-compartment model in which there are well-mixed body and hepatic water pools.[2] In this study, we further analyze this model and compare predictions of ethanol metabolism obtained with the one- and two-compartment models, particularly emphasizing the differences predicted for FPM.

Two-Compartment Model

Figure 2 shows the basic model we have used previously.[2] Two well-stirred compartments—liver water and body water—are connected by hepatic blood flow. The body water and liver compartments are characterized by ethanol concentrations (C_B and C_L, respectively) and volumes of ethanol distribution (V_B and V_L). The rate of input of ethanol (Q) can be either via the intravenous route (Q_{IV}) into the body water compartment or a gastrointestinal route (Q_{GI}) directly into the liver compartment. (First-pass metabolism in the gastrointestinal mucosa will be considered to be negligible, such that absorption rate from the gut equals the rate of hepatic delivery of newly absorbed ethanol.) Total hepatic blood flow equals the rate of flow in the hepatic vein (F_{HV}). Concentrations in the two-compartments are described by the following two differential equations:

$$V_B(dC_B/dt) = F_{HV}(C_L - C_B) + Q_{IV} \quad (2)$$

$$V_L(dC_L/dt) = F_{HV}(C_B - C_L) + Q_{GI} - V_{max}C_L/(K_m + C_L) \quad (3)$$

Although the activity of ADH may be influenced by factors such as the NADH and acetaldehyde concentrations,[3] our initial calculations assumed that liver metabolism follows simple initial rate Michaelis-Menten kinetics, and that there is negligible extrahepatic metabolism or excretion of ethanol. The solution to these equations is obtained numerically using a fourth-order Runge-Kutta routine with adaptive step size control.[4]

Parameters used in the model for an 80 kg subject were: F_{HV} = 1.5 liters/min (consisting of typical values for portal vein and hepatic artery flows of 1,000 ml/min and 500 ml/min, respectively)[5]; V_B = 48 liters (60% of body weight); and V_L = 0.61 (60% of a 1 kg liver). The V_{max} was assumed to be the metabolic rate of 2.75 mmol/min/80 kg observed during the constant ethanol elimination phase of the data of Wilkinson et al.,[1] who assessed blood ethanol concentrations at frequent intervals during and after a 2-hr constant intravenous ethanol infusion in six male subjects. The K_m was the value that, when substituted with the other parameters into the above set of differential equations, provided the best fit to the observed elimination data of Wilkinson et al. A very good fit was provided for the two-compartment model by a K_m of ~0.1 mM (Fig. 1). This K_m, which is far lower than the approximate 2 mM values used in one-compartment models, is of the same order of magnitude of previously reported in vivo estimates of the true K_m (0.14 mM for humans,[6] 0.27 mm for pigs,[6] and 0.33 mM for dogs[7]). Support for the accuracy of the model and the parameter values was provided by a recent study in which we measured gastrointestinal absorption of ethanol in five subjects and applied these absorption data to the model.[8] There was a relatively close fit between predicted and observed blood ethanol values.

The excellent fit between the metabolic rate predicted by the model and the observed metabolic rate indicates that modifications of Michaelis kinetics, such as the influence of NADH or acetaldehyde concentrations, apparently do not need to be used. It should be cautioned, however, that the model was tested over a range of blood ethanol concentrations spanning 12 mM to ~0.2 mM. It is possible that alterations in kinetics occur at higher blood ethanol concentrations due a variety of factors, such as product inhibition or the action of high K_m enzymes that might alter the value for V_{max}. Thus, the accuracy of the model at blood ethanol concentrations of >12 mM will require additional validation experiments.

There are two major simplifications in our model's assumption that the liver can be represented as a single well-mixed compartment. First, liver blood flow per unit volume may not be uniform, with some regions receiving

Table 1. Effect of Hepatic Ethanol Metabolism Calculated from the One-Compartment Model on the Concentration of Ethanol in the Liver

[Ethanol] entering liver (mM)	Hepatic delivery of ethanol (mmol/min)	Metabolism predicted* (mmol/min)	[Ethanol] exiting liver (mM)	Metabolism predicted at exiting [ethanol]† (mmol/min)
0.5	0.75	0.78	−0.03	Negative
1.0	1.5	1.29	0.14	0.26
3.0	4.5	2.25	1.5	1.63
6.0	9.0	2.78	4.1	2.50
9.0	15.0	3.06	8.0	2.92

* Metabolism was calculated from Eq. 1 of text using values for K_m of 1.8 mM and V_{max} of 3.6 mmol/min as reported by Wilkinson et al.,[1] assuming that hepatic ethanol concentration equals the entering blood ethanol concentration and an hepatic blood flow of 1500 ml/min.

† Metabolism calculated as described assuming hepatic ethanol concentration equals exiting blood ethanol concentration.

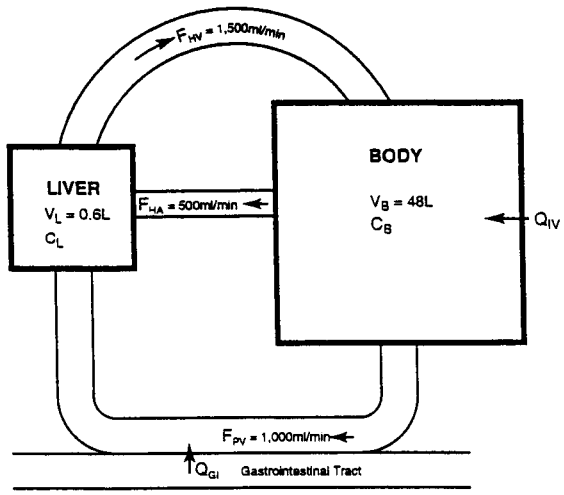

Fig. 2. Two-compartment model used to calculate first-pass metabolism of ethanol (see text for description of various parameters).

higher or lower than average flows. The magnitude of this effect has been determined in the in situ perfused canine liver by directly measuring the perfusion heterogeneity of D_2O.[9] The coefficient of variation of the local perfusion rate of ~0.5 produced about a 15% higher venous D_2O outflow concentration than would be expected with uniform perfusion. This should represent the maximum influence of heterogeneity, because these measurements were made in anesthetized dogs after surgical manipulations, conditions that presumably might increase perfusion heterogeneity. In addition, errors due to uniform flow would be minimized by our choice of K_m value, which represents something resembling a weighted average over the heterogeneous liver. The second assumption of the model is that each local hepatic unit is well-stirred. Significant gradients in ethanol concentration could exist along the length of the sinusoid. The extreme limit of this situation is the linear model originally proposed by Goresky et al.,[7] in which there is perfect mixing radial to the sinusoid and no mixing parallel to the sinusoid. Lifson et al.[10] compared the predicted D_2O venous outflow curves for the two models using the directly measured flow heterogeneity and concluded that the well-mixed model provided a slightly better fit to the observed data. Presumably, the actual situation in the liver appears to be intermediate between the well-mixed and linear models.

Goresky et al.[11] have published a detailed analysis of ethanol metabolism in the canine liver using the linear model and incorporating heterogeneity of both blood flow and transit time. We attempted to assess the magnitude of the error that might be introduced by our use of a well-stirred model of metabolism in the human liver, by comparing the steady-state solution for the rates of ethanol metabolism predicted for the linear versus the well-mixed model (see Appendix). The differences in the two models were small, with a maximum difference of ~7% (Goresky model larger). Thus, whereas our assumption of a perfectly mixed liver compartment is an oversimplification, potential errors resulting from this assumption seemingly should be relatively minor.

Comparison of Ethanol Metabolism Predicted by One- and Two-Compartment Models

For the two-compartment case in the steady state, the relation between the blood concentration and the rate of intravenous ethanol infusion (Q_{IV}) is described by Eq. 4:

$$F_{HV}(C_B - C_L) = Q_{IV} = V_{max}C_L/(K_m + C_L), \qquad (4)$$

where

$C_L = 0.5[-b + \sqrt{b^2 + 4C_BK_m}]$ and $b = K_M - C_B + (V_{max}/F_{HV})$

The two-compartment model used a K_m of 0.1 mM and a V_{max} of 2.75 mmol/min, obtained as described previously. Metabolism with the one-compartment model was calculated from Eq. 1, assuming $C_L = C_B$, a K_{app} of 1.8 mM, and a V_{max} of 3.6 mmol/min, the values reported by Wilkinson and coworkers[1] to provide the best fit (in the one-compartment model) to the observed elimination data shown in Fig. 1.

Theoretically, the two models might be expected to have the same V_{max}, because this value should be independent of the modeling. However, with the one-compartment model, an artificially high K_m is required to roughly fit the observed data at low blood ethanol concentration. This high K_{app}, in turn, requires the use of an artifactually high V_{max}. The V_{max} of 3.6 mmol/min, which provided the best fit to the one-compartment model, is ~30% higher than the metabolic rate observed during the linear phase of ethanol elimination (2.75 mmol/min), the rate that presumably represents the true V_{max}.

Figure 3 compares the steady-state relationship between

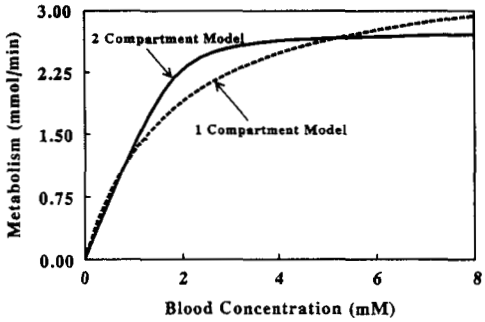

Fig. 3. Predicted steady-state relationship between blood ethanol concentration and the rate of ethanol metabolism by the liver. The two curves show the relationships predicted by the two-compartment model and a one-compartment model (see text for parameters of models).

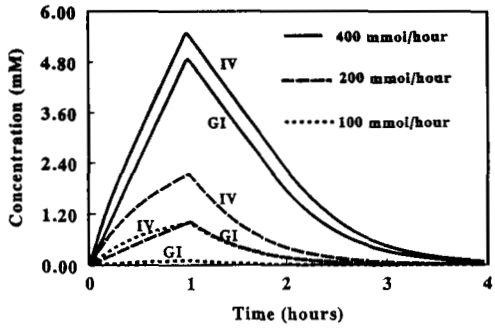

Fig. 4. Blood ethanol curves predicted by the two-compartment model (see text) for 1 hr intravenous (IV) or portal [gastrointestinal (GI)] infusions of ethanol in doses of 100 mmol, 200 mmol, or 400 mmol.

the blood ethanol concentration and predicted hepatic metabolism for one- and two-compartment modeling of the observed elimination data in Fig. 1. A major difference in the predicted curves is that near-total saturation occurs much more abruptly and at a much lower blood ethanol concentration (~3.0 mM) with the two-compartment model. Given the K_{app} of a blood ethanol concentration of ~1.8 mM in the one-compartment model, a continually increasing ethanol metabolism would be expected over the range of blood ethanol levels commonly obtained in experimental studies in humans, which seldom exceed 14 mM. For example, ethanol metabolism should be 31% and 40% greater at blood ethanol concentrations of 8 mM and 14 mM, than at 3 mM. Thus, if this model were correct, what appears to be linear decline in serum ethanol concentration in experimental studies could not truly be linear. For this reason, the seemingly near-perfect linear decline in blood ethanol commonly has been declared to be "pseudolinear." As shown in Fig. 3, with the two-compartment model, metabolism is predicted to be ~95% of maximal at a blood ethanol concentration of 3 mM. Thus, this model predicts that the decline in blood ethanol from high levels to ~3 mM should be very nearly "linear."

Quantitation of First-Pass Metabolism

For a substance that is eliminated with first-order kinetics, FPM can be defined as the decrease in peripheral availability (PA) that results from presystemic metabolism in the gut mucosa or liver. Defining FPM for a compound that is removed primarily via zero order kinetics (as is the case with ethanol) is somewhat more complicated. Consider the case of ethanol absorption from the gut occurring when the ethanol concentration in systemic blood is sufficiently high to saturate hepatic metabolism. Some of the newly absorbed ethanol molecules will undergo metabolism during the first pass through the liver. However, this hepatic metabolism simply displaces metabolism of systemic ethanol. In this situation, the infusion of additional ethanol via either a systemic vein or the portal vein (i.e., via gut absorption) results in a similar increase in peripheral ethanol, and presystemic metabolism has no influence on PA of ethanol. Thus, when elimination is not first-order, biologically relevant FPM has to be defined solely as the quantitative influence of presystemic metabolism on PA. It should be stressed that the efficiency of so-defined FPM for a given quantity of newly absorbed ethanol is critically dependent on the peripheral blood ethanol concentration. At low blood ethanol concentrations, small quantities of newly absorbed alcohol may undergo virtually complete FPM, whereas at high blood ethanol levels FPM will be negligible.

Blood ethanol concentrations expected from the gut absorption versus an intravenous infusion of ethanol can be predicted from the two-compartment model by solving the set of differential equations (Eqs. 2 and 3), as alcohol is "fed" at the desired rate directly into the liver or the body water compartments of the model. Figure 4 shows the predicted peripheral blood ethanol curves produced by 100, 200, or 400 mmol of ethanol constantly delivered over 60 min via infusion into a peripheral vein or absorption from the gastrointestinal tract (assuming no metabolism in the gastrointestinal mucosa). The most striking feature of these data is the marked nonlinear dependence of the blood ethanol values on portal ethanol input. At low rates of infusion, only a small fraction of gastrointestinally absorbed ethanol reaches the peripheral circulation, while at high rates of infusion, almost all of this ethanol reaches the peripheral circulation (i.e., near-comparable blood levels are obtained with portal versus intravenous infusion routes). At the low infusion rates, liver concentration remains low, the ADH is unsaturated, and very little ethanol escapes the liver. Thus, the fraction of ethanol entering the liver from the peripheral circulation remains small, compared with the portal input, and the bulk of ethanol metabolism is conducted on newly absorbed ethanol. As the rate of ethanol input increases, the liver enzyme becomes saturated, most of the ethanol escapes the liver, and the peripheral blood ethanol concentration rises and "competes" for metabolism with newly absorbed ethanol.

The quantity of ethanol undergoing FPM can be predicted from the two-compartment model, provided the absorption rate of ethanol is known with precision. As discussed previously, functional FPM (i.e., FPM that enhances

Table 2. Predicted First-Pass Metabolism of Varying Doses of Ethanol Administered as a Constant Infusion Over 1 Hr

Input rate (mmol/hr)	Input route	Total amount metabolized over 4 hr (mmol)	AUC (mmol × hr)	FPM calculated from two-compartment model		FPM calculated from AUC difference (%)
				mmol	%	
100	GI	100	0.13	88	88	89
	IV	100	1.19			
200	GI	200	1.11	107	53	57
	IV	199	2.59			
400	GI	397	6.74	40	10	18
	IV	396	8.18			

GI, gastrointestinal (portal); IV, intravenous.

PA) occurs only when the direct hepatic delivery of newly absorbed ethanol enhances the rate of metabolism that would otherwise occur simply due to the recirculation of systemic ethanol. To determine the rate of metabolism supported by recirculating ethanol, it is necessary to identify a recirculating hepatic ethanol concentration (C_R), which represents the hepatic concentration of ethanol that would exist if the only source of hepatic ethanol were systemic ethanol. This concentration is described by a third differential equation:

$$V_L(dC_R/dt) = F_{HV}(C_B - C_R) - V_{max}C_R/(K_m + C_R). \quad (5)$$

This equation states that the change in liver ethanol concentration (C_R) resulting from recirculation of previously absorbed ethanol equals the rate of inflow of recirculating ethanol minus the rate of egress of this ethanol via the hepatic vein, and the rate of metabolism expected if the only ethanol in the liver were this recycled ethanol. FPM then is defined as the *extra* metabolism that occurs at any moment because the concentration of ethanol in the liver (C_L) (the sum of C_R plus the hepatic concentration derived from newly absorbed ethanol) produces more rapid metabolism than does C_R. The limiting case is a fully saturating C_R, where there can be no increase in metabolism, hence no functional FPM, even though C_L might be much greater than C_R due to hepatic delivery of newly absorbed ethanol. Thus:

$$\text{FPM} = \int\left[\frac{V_{max}C_L}{K_m + C_L} - \frac{V_{max}C_R}{K_m + C_R}\right]dt, \quad (6)$$

where the integral is over the time period of interest. The first term in the integral is the total liver metabolism, and the second is the metabolism of the recycled component.

Determination of FPM from Blood Ethanol Curves

Publications continue to appear in which FPM is determined from the difference in area under blood ethanol concentration curves (AUC) obtained after intravenous and oral administration of similar doses of ethanol.[12–14] However, AUC is an accurate indicator of peripheral availability only when elimination is first order. For compounds eliminated primarily via zero-order kinetics, AUC differences tend to grossly overestimate the fraction of the dose that undergoes FPM. Table 2 lists the "exact" FPM calculated from Eq. 6 for the three ethanol inputs shown in Fig. 4. As was evident qualitatively, FPM is very nonlinear, decreasing from 88% to 10% of the total metabolism for constant 1 hr inputs via the portal vein of 100 and 400 mmol of ethanol, respectively. Table 2 also lists the percentage FPM estimated from the difference between the AUC's predicted for intravenously and portally administered ethanol. At the 100 mmol/hr infusion rate, the 89% FPM calculated by AUC difference is very close to the value obtained with two-compartment model, whereas for the 400 mmol/hr infusion, the AUC percentage difference is 18%, as opposed to the model's prediction of an FPM of 10%. The ability of the AUC difference to accurately quantitate FPM with the 100 mmol/hr infusion rate is attributable to the nearly total first-order kinetics of elimination with this very slow infusion rate. As the infusion rate is increased, elimination becomes zero order, and the AUC difference becomes an inaccurate indicator of FPM.

It is important to realize that a faster rate of absorption of identical doses of ethanol may result in both: (1) a true decrease in FPM and (2) a disproportionate increase in AUC that gives the incorrect impression of a much greater reduction in FPM than is actually the case. The rationale for the initial claims that the stomach was the major site of first-pass metabolism of ethanol was largely based on the much greater AUC's observed when ethanol was instilled intraduodenally[15] or intraportally[16] versus into the stomach. In reality, the AUC differences are readily explained by the much more rapid absorption of ethanol in the experiments where the stomach was bypassed.

As shown herein, FPM can be predicted from the two-compartment model if the exact rate of ethanol absorption (Q_{GI} in Eq. 3) is known throughout the course of the experiment; however, in most human studies, the only available information is the blood ethanol concentration curve resulting from a given dose of ethanol. As originally described by Wilkinson et al.,[17] the PA of ethanol can be calculated from the blood ethanol curve by assuming that PA equals the total quantity of peripheral ethanol metabolized. This metabolism is calculated by integrating the metabolism predicted for the blood ethanol concentrations observed over the entire extent of the blood ethanol curve. The difference between the total dose of ethanol adminis-

tered and the PA of the orally administered ethanol (which is assumed to be totally absorbed) corresponds to the quantity undergoing FPM.

With the one-compartment model, FPM is calculated from the following formula as described by Lim and coworkers[18]:

$$(\text{FPM}) = A - V_B C_B(t) - \int_0^t \frac{V_{\max} C_B}{K_{\text{app}} + C_B}\, dt, \qquad (7)$$

where A equals the total dose (absorption is assumed to be complete), $V_B C_B(t)$ equals the quantity of ethanol remaining in the body water pool, and the term in the integral describes the rate of ethanol metabolism as a function of the observed blood concentration.

For the two-compartment model, FPM can be estimated from:

$$(\text{FPM})_{\text{est}} = A - V_B C_B(t) - V_L C_a(t) - \int_0^t \frac{V_{\max} C_a}{K_m + C_a}\, dt \qquad (8)$$

$$C_a = 0.5[-b + \sqrt{(b^2 + 4C_B K_m)}] \qquad b = K_m - C_B + (V_{max}/F_{HV})$$

The first two terms in this expression are similar to that described for the one-compartment model, and the third term is the ethanol present in the hepatic water pool. The integral represents the component of the metabolism that results from recirculated ethanol. The term C_a is the steady-state approximation to the C_R term used in the exact expression for first pass metabolism (see Eq. 6). This steady-state limit (C_a) is a very good approximation to the exact time-dependent term (C_R), differing by only ~1% (data not shown).

If the blood ethanol measurements are conducted for a time period sufficient for the blood concentration to fall to a very low value, the body water distribution term in Eqs. 7 and 8 and the hepatic water distribution term of Eq. 8 become negligible. Thus, in each of the models, FPM is calculated as the difference between the total administered dose and the total calculated metabolism of peripheral ethanol. The accuracy of this technique depends on the accuracy with which the rate of ethanol metabolism can predict over the range of blood ethanol concentrations observed. Estimation of FPM by the two models will differ to the extent that the predicted rate of metabolism of peripheral ethanol differs for the two models, as graphically depicted in Fig. 3.

In many published studies, blood ethanol levels have been compared after oral and intravenous administration of the same amount of ethanol to the same subjects. By definition, an intravenous infusion has 100% PA. Thus, when data for both intravenous and oral administration are available, an alternative definition of FPM is:

$$\text{FPM} = \text{PA}_{\text{IV}} - \text{PA}_{\text{Oral}}, \qquad (9)$$

where both measurements of PA are for the same ethanol dose. Equation 9 provides a more accurate estimate of FPM than Eq. 8, because errors in parameters alter both the terms on the right-hand side of Eq. 9 in approximately the same way. For example, consider the data for the constant infusion of 400 mmol over 1 hr (Fig. 4). The PA of the oral dose (determined from the blood concentration curve with the two-compartment model) is 360 mmol, so that the true FPM is 40 mmol. Erroneously using values that are 20% too small for K_m, $V_{\max}$ and F_{HA} yields a PA of 303 mmol. The corresponding FPM determined from Eq. 8 would be 97 mmol, 2.4 times larger than the true value. In contrast, if PA for the intravenous blood curve in Fig. 4 (determined with the incorrect parameters) is used in Eq. 9, one obtains a FPM of 31.4 mmol, a much better estimate of the true value (40 mmol). Using the curves in Fig. 4 may appear to be an ideal application of Eq. 9, because both the intravenous and gastrointestinal infusions were at identical rates, a situation that does not occur in clinical studies. However, when PA for an intravenous dosage is calculated for a 400 mmol dose infused over just 10 min, the FPM estimated from Eq. 9 is 29.4 mmol, still a reasonably good estimate. This example illustrates that Eq. 9 provides a robust estimate of FPM that is relatively independent of the assumed values of the two-compartment model parameters. This last calculation shows that the more rapid rise in blood ethanol and the higher peak value resulting from the more rapid ethanol infusion had only a minimal effect on the value of integral in Eq. 8 that predicts PA and FPM. A corollary of this observation is that incomplete mixing of ethanol in the body water compartment should not appreciably corrupt the calculation of PA or FPM. This is of some importance because early in the time course of an ethanol infusion or gastrointestinal absorption, the blood ethanol level may be appreciably higher than predicted due to heterogeneity of perfusion in the body compartment.

Appreciably different estimates of FPM are obtained when published blood ethanol data are determined using AUC differences, the one-compartment, and the two-compartment models of metabolism. For example, Fig. 5 shows the approximate blood ethanol curves reported for subjects ingesting 0.3 g/kg of ethanol, before and during treatment with aspirin.[19] The AUC determined during aspirin treatment (11.1 mM × h) was 21% greater than in the absence of aspirin (8.8 mM/L × h), and the authors suggested that aspirin reduced FPM by ~21%. Table 3 lists the approximate peripheral ethanol metabolism predicted by the one- and two-compartment models for each time interval of the blood ethanol curves of Fig. 5. With the two-compartment model, PA was only 2.5% greater for the aspirin versus the control period (i.e., aspirin actually had a negligible effect on FPM). The sizable difference in AUCs simply reflects the slightly more rapid absorption of ethanol with aspirin treatment, presumably secondary to more rapid gastric emptying. When PA of ethanol was calculated from the one-compartment model (K_{app} of 1.78 mM and a

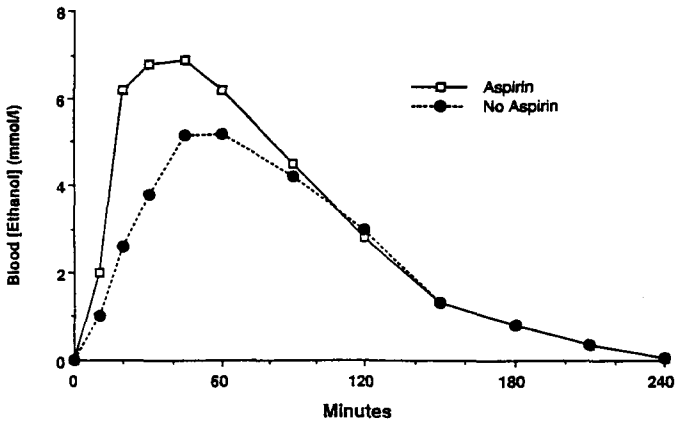

Fig. 5. Approximate blood ethanol curves observed by Roine et al.[19] when 0.3 g/kg of ethanol was ingested by subjects before or during aspirin treatment.

V_{max} of 3.58 mmol/min[1]), there was a 8.2% greater peripheral availability during the aspirin treatment. This 3-fold greater difference in FPM when estimated by the one- versus two-compartment model reflects the difference in configuration of the blood ethanol concentration versus hepatic metabolism curves of the two models (Fig. 3). The metabolism predicted by the two-compartment model plateaus at a blood ethanol concentration of 3 mM. Thus, the sizable differences in blood ethanol levels between 20 and 90 min of the curves shown in Fig. 5 do not translate into appreciably increased metabolism (Table 3), because the concentration was >3 mM for both oral and intravenously administered ethanol. The higher K_m (K_{app}) of the one-compartment model predicts that ethanol metabolism should increase as the blood ethanol concentrations up to levels of 8 mM and higher (Fig. 3, Table 3). Thus, the one-compartment model predicts greater differences in peripheral ethanol metabolism (and FPM) between the blood ethanol curves depicted in Fig. 5.

Ranitidine therapy has been alleged to inhibit FPM of ethanol in the stomach and produce clinically relevant increases in peripheral availability of ethanol. Data initially used to support this concept are approximated in Fig. 6, which shows the blood ethanol curves obtained when 0.3 g/kg ethanol was administered orally (with a meal) or intravenously, before or during treatment with ranitidine.[20] The much lower blood ethanol levels observed with oral versus intravenous administration (AUC difference = 34%) in the absence of ranitidine gives the impression of a sizable FPM. The nearly comparable blood ethanol curves during ranitidine treatment suggests near elimination of FPM. The authors analysis of these data with a one-compartment model yielded a FPM of 23% without ranitidine and 13% with ranitidine. However, calculations with the two-compartment model showed that, in the control (no ranitidine) experiments, the PA of oral ethanol was only 10.5% less than that with intravenous ethanol (i.e., FPM was only 10.5%). With ranitidine treatment, FPM was 6.4%, yielding a trivial 4% increase in PA of ethanol possibly attributable to the action of ranitidine. A general message of the above analysis is that, even when FPM is maximized via the ingestion of ethanol with a large meal (which slows gastric emptying), only ~10% of a small dose of ethanol (0.3 g/kg) undergoes FPM. Thus, inhibition of FPM can have only a minor influence on the peripheral availability of this dose of ethanol.

Analysis of published blood ethanol curves after oral and intravenous administration of ethanol showed that claims concerning FPM based on AUC differences almost always grossly overestimated what we believe to be the "true" FPM calculated from the two-compartment model. Values for FPM calculated from a one-compartment model yielded variable overestimates of the "true" value. Major differences between the FPM predicted by the two models occurred when blood ethanol concentrations with oral dosing were in the 2.5 mM to 5 mM range for an extended period. During this period, peripheral ethanol metabolic rates are similar for oral and intravenous ethanol when determined by the two-compartment model, whereas appreciable differences in metabolism are predicted by the one-compartment model. An example of the potential discrepancy that may exist between the FPM predictions of

Table 3. Peripheral Ethanol Metabolism Calculated from Application of One- and Two-Compartment Models to Blood Ethanol Curves Obtained in Subjects Ingesting Ethanol, On or Off Aspirin (ASA) Treatment (Fig. 5)

Interval (min)	Ethanol metabolized (mmol)			
	Two-compartment model		One-compartment model	
	No ASA	ASA	No ASA	ASA
0–10	7.5	12.5	6.3	12.5
10–20	23.0	26.0	17.8	25.5
20–30	26.2	27.2	22.6	28.6
30–45	39.7	40.8	38.2	42.6
45–60	39.9	40.0	39.9	43.1
60–90	79.8	80.4	76.5	80.6
90–120	78.0	79.8	66.0	66.0
120–150	72.0	70.5	60.0	61.0
150–180	42.0	42.0	39.0	39.0
180–210	19.0	19.0	20.1	20.1
210–240	8.9	8.9	9.0	9.0
0–240	436.0	447.1	395.4	428.0

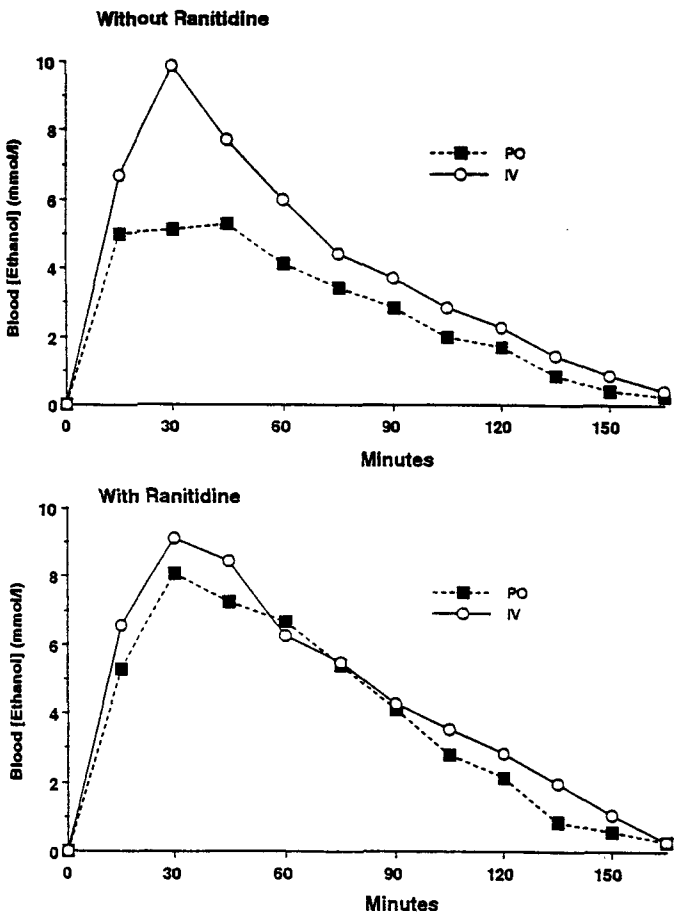

Fig. 6. Approximate blood ethanol curve reported by DiPadova et al.[20] when 0.3 g/kg of ethanol was administered intravenously or orally to subjects before or during ranitidine treatment.

the two models was observed in a study in which a group of females ingested 0.3 g/kg dose of ethanol with food.[21] The authors, using a one-compartment model, reported 24.4% FPM, whereas our two-compartment model indicated only ~9.5% FPM.

Analysis of published data with the two-compartment model showed that FPM was 50% to 66% for a 0.15 g/kg dose of ethanol ingested with food[8,22] and only ~3% when this dose was taken without food.[8] With increasing ethanol dosage, FPM falls precipitously to ~10% for a 0.30 g/kg dose taken with food.[20,21,23] FPM should be negligible for a dosage of >0.4 g/kg (roughly two bottles of beer). Thus, FPM is not an important determinant of the blood ethanol levels that result from ingestion of potentially inebriating doses of ethanol.

APPENDIX: COMPARISON OF LINEAR AND WELL-STIRRED LIVER MODELS IN STEADY STATE

In the liver, the sinusoids are arranged in parallel, and their inflow and outflow ports tend to be aligned with their neighbors. Given the rather long length of the sinusoids (~500 μm) relative to the radius of tissue supplied by each sinusoid (~50 μm), large variations in ethanol concentration along the axial position of the sinusoid could exist, invalidating the well-stirred assumption of our model. As a limiting case of this distribution, Goresky[11] assumed that diffusion radial to the sinusoid was infinitely fast and that axial diffusion was 0. The ethanol distribution for this model is analogous to a chromatography column, with the ethanol uniformly distributed along a given plane and advancing with a sharp front down the column carried by the blood flow F. For this model, the steady-state concentration C as a function of the distance x along the sinusoid is described by the differential equation:

$$FL(dC/dx) = V_{max}C/(K_m + C), \quad \text{(A1)}$$

where L is the length of a sinusoid. This equation has the boundary condition that at $x = 0$, $C = C_B$. This first-order nonlinear ordinary differential equation has the following exact solution that was obtained using the integrating factor method[24]:

$$C \exp[C/K_m + x/b] = C_B \exp[C_B/K_m]$$

$$b = FKmL/V_{max}. \quad \text{(A2)}$$

The concentration leaving the sinusoid at the venous end (C_V) is then equal to C at $x = L$ and is described by the equation:

$$C_V \exp[C_V/K_m + V_{max}/(FK_m)] = C_B \exp[C_B/K_m]. \quad \text{(A3)}$$

The rate of steady-state ethanol metabolism (Q) is then equal to the difference between the rate inflow and outflow of ethanol:

$$Q = F(C_B - C_V), \quad \text{(A4)}$$

where C_V is obtained from the solution of Eq. A3. Figure A1 compares the steady-state rate of metabolism for the well-stirred model (Eq. 5) versus that for the Goresky model (Eq. A4) as a function of blood concentration. For the data in this figure, Eq. A3 was solved using Brent's method.[24] The differences in the steady-state rate of ethanol metabolism for the two models is surprisingly small, given the marked differences in the basic assumptions of the models. The steady-state limit is the appropriate situ-

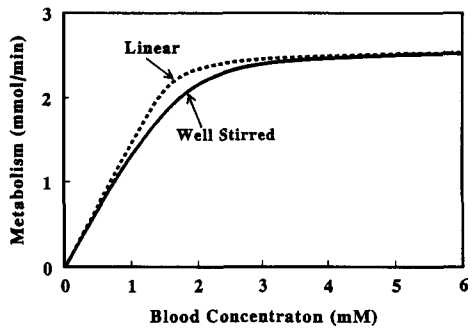

Fig. A1. Steady-state relationship between blood ethanol concentration and the hepatic metabolism of ethanol calculated with the two-compartment model. The two curves show the results obtained with well-stirred hepatic water and the model of Goresky[11] in which there is no stirring along the linear axis of the sinusoid and perfect equilibration radially.

ation to compare the two models, because, as was described in the text, this limit is a very good approximation to the time dependent solution. Although the actual liver is probably somewhere intermediate to the well-stirred and Goresky model, the small differences obtained in Fig. A1 indicate that minimal error is introduced by the use of the well-stirred model.

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