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Evaluating Toxicology Evidence in Transdermal Alcohol (SCRAM) Monitoring

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The kinetics of transdermal ethanol exchange

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Anderson, Joseph C., and Michael P. Hlastala. The kinetics of transdermal ethanol exchange. *J Appl Physiol* 100: 649–655, 2006. First published October 20, 2005; doi:10.1152/japplphysiol.00927.2005.—The kinetics of ethanol transport from the blood to the skin surface are incompletely understood. We present a mathematical model to predict the transient exchange of ethanol across the skin while it is being absorbed from the gut and eliminated from the body. The model simulates the behavior of a commercial device that is used to estimate the blood alcohol concentration (BAC). During the elimination phase, the stratum corneum of the skin has a higher ethanol concentration than the blood. We studied the effect of varying the maximum BAC and the absorption rate from the gut on the relationship between BAC and equivalent concentration in the gas phase above the skin. The results showed that the ethanol concentration in the gas compartment always took longer to reach its maximum, had a lower maximum, and had a slower apparent elimination rate than the BAC. These effects increased as the maximum BAC increased. Our model's predictions are consistent with experimental data from the literature. We performed a sensitivity analysis (using Latin hypercube sampling) to identify and rank the importance of parameters. The analysis showed that outputs were sensitive to solubility and diffusivity within the stratum corneum, to stratum corneum thickness, and to the volume of gas in the sampling chamber above the skin. We conclude that ethanol transport through the skin is primarily governed by the washin and washout of ethanol through the stratum corneum. The dynamics can be highly variable from subject to subject because of variability in the physical properties of the stratum corneum.

diffusion; convection; blood alcohol concentration; skin alcohol; SCRAM

ACCURATE QUANTIFICATION OF alcohol concentration in the body is important in both forensic and physiological research applications. The most accurate and reliable method is direct blood sampling and analysis by gas chromatography. The alcohol breath test is commonly used because of its noninvasive and indirect approach. The measurement is not continuous, which makes it difficult to follow the pharmacokinetics of the blood alcohol concentration (BAC) and inaccurate due to the variability in delivery of the sample in different subjects (14).

The pharmacokinetics of alcohol are complex because of the intricate nature of the distribution into the various watery tissues in the body. The kinetics are dependent on absorption from the intestine into the blood, elimination from the blood via metabolism in the liver, and transport in different tissue compartments via diffusion and convection. This balance between absorption and elimination of alcohol is reflected in the BAC. After a drink, the BAC rises until absorption is complete. After a maximum in BAC is achieved, the BAC decreases during the "burn-off" or elimination phase primarily due to metabolism in the liver.

In legal cases involving the use of alcohol, courts may require abstinence until the matter is resolved in a legal proceeding. In the past, abstinence has been monitored with random breath testing, which leaves the possibility that a drinking event might be missed. The recent development of the SCRAM device (secure continuous remote alcohol monitor; Alcohol Monitoring Systems, Highlands Ranch, CO) (12) shows promise as a means for measuring a pseudocontinuous supradermal ethanol concentration, ethanol concentration in the gas space above the skin, at multiple points in time as a means for identification of violation of abstinence from alcohol. The SCRAM device is an ankle bracelet that simultaneously measures skin temperature and ethanol vapor above the skin surface. Ethanol arrives at the skin surface via passive alcohol diffusion from blood flowing through skin capillaries (insensible perspiration) and perspiration due to secretory activity of sweat glands (sensible perspiration). The alcohol concentration in an air sample taken from just above the skin surface vs. time is analyzed as a means of estimating BAC as a function of time. Only minimal information regarding the design and functional features of the SCRAM device is available in the literature. Thus we have chosen to focus on the kinetics of alcohol diffusion from the blood, through the skin, and into a generic measurement device lying on the surface of the skin.

It has been assumed that the shape of the supradermal ethanol concentration curve mimics the shape of the BAC curve. This interpretation may fail to recognize physiological variation in the process of diffusive transport through the skin, resulting in either false positive or false negative findings of alcohol consumption. This paper seeks to define the important factors governing the relationships between the BAC vs. time curve and the supradermal ethanol concentration vs. time curve. Additionally, this paper intends to evaluate the physiological limitations to interpretation of supradermal ethanol concentration data. In the present study, we develop a mathematical model of ethanol transport through the skin. Using this model, we explore how the time-varying concentration of ethanol in the blood affects the ethanol concentration above the skin. Additionally, a sensitivity analysis using Latin hypercube sampling (LHS) is implemented to reveal how variability in tissue, blood, and gas parameters affect skin ethanol concentration. These analyses answer the following two questions. Why is the supradermal ethanol concentration delayed and attenuated relative to the ethanol concentration in the blood? What factors are most responsible for this attenuation?

METHODS

Mathematical model. To simulate ethanol exchange across the skin surface, we chose a model consisting of four compartments: blood, epidermis, stratum corneum, and gas (Fig. 1). Dissolved ethanol in the

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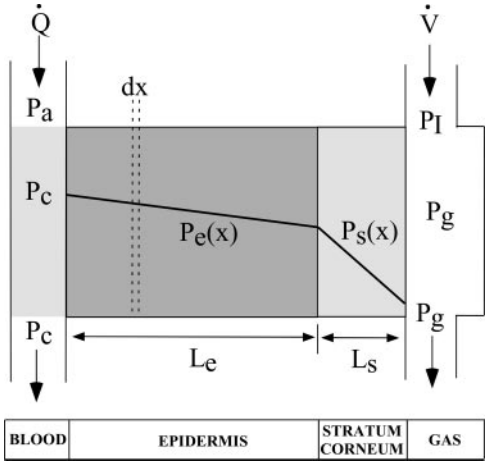

Fig. 1. Schematic showing a cross-section of skin next to a device for measuring supradermal ethanol concentration. Ethanol entering the system via the blood diffuses through the epidermis and stratum corneum before entering the gas compartment and is removed from the system by convective gas flow ($\dot{V}$). A differential length (dx) was used for mathematical analysis. Pa, Pc, P_e, P_g, P_s, arterial, capillary, epidermal, gas, and stratum corneum ethanol partial pressures, respectively. See Table 1 for more definitions.

blood) is delivered to the skin via blood flow through the capillaries. Ethanol enters and leaves the capillaries at partial pressures Pa and Pc, respectively. Ethanol diffuses through the epidermis and the stratum corneum before it reaches the gas phase, which is ventilated with fresh air. As a first approach, we focused only on diffusional transport through the tissue layers. We neglected any transport resulting from sensible perspiration (i.e., sweating). We assumed that the capillary and gas compartments were individually well mixed and that uniform diffusion occurred across the epidermis and stratum corneum.

Similar to the model of vanLöbensels et al. (29), we used four coupled differential equations to describe mass transport between blood, epidermis, stratum corneum, and gas. *Equation 1* represents the rate of change of mass of a dissolved gas in the capillary blood compartment. It is equal to the rate of gas delivery to the capillary space via blood flow, the rate of gas removal via blood flowing out of the capillary, and the rate of diffusive gas flux across the capillary membrane into the epidermis. P_e is the partial pressure of ethanol in the epidermis. See Table 1 for parameter definitions.

$$\beta_b A_c L_c \frac{\partial Pc}{\partial t} = \dot{Q}\beta_b(Pa - Pc) - D_e\beta_e A_c \left.\frac{\partial P_e}{\partial x}\right|_{x=0} \quad (1)$$

Equations 2 and *3* describe diffusion in the epidermis and stratum corneum, respectively.

$$\beta_e A L_e \frac{\partial P_e}{\partial t} = D_e\beta_e A L_e \frac{\partial^2 P_e}{\partial x^2}, \quad 0 \le x < L_e \quad (2)$$

$$\beta_s A L_s \frac{\partial P_s}{\partial t} = D_s\beta_s A L_s \frac{\partial^2 P_s}{\partial x^2}, \quad L_e < x \le L_e + L_s \quad (3)$$

P_s is the partial pressure of ethanol in the stratum corneum. Between the epidermis and stratum corneum, we imposed that the flow of gas between the epidermis and stratum corneum was equal.

$$D_e\beta_e \frac{\partial P_e}{\partial x} = D_s\beta_s \frac{\partial P_s}{\partial x} \text{ at } x = L_e \quad (4)$$

Equation 5 represents an enclosed air space above the skin. The rate of change of gas in this compartment is determined by addition of gas from the ambient air ($P_I = 0$), subtraction of gas removed by fresh air ventilation, and addition of gas diffusing across the air-skin interface from the stratum corneum, adjacent to the compartment.

$$\beta_g A L_g \frac{\partial P_g}{\partial t} = \dot{V}\beta_g(P_I - P_g) + D_s\beta_s A \left.\frac{\partial P_s}{\partial x}\right|_{x=L_e+L_s} \quad (5)$$

where P_g is the partial pressure of ethanol in the gas compartment. The section *Parameter estimates*, below, defines and presents average values for all model parameters.

We solved the system of four partial differential equations numerically to determine the partial pressure profiles in the epidermis and stratum corneum and the partial pressure of ethanol in the gas compartment as a function of time given a time-varying Pa of ethanol. Spatial derivatives were solved by upwind finite difference, and time derivatives were solved using LSODE, a time-integrating algorithm developed by Hindmarsh (13). The executable program was submitted as a batch job in which each simulation was solved numerically using an Intel Pentium IV computer running Digital Visual Fortran. Pc and Pg are equal to $P_e(0)$ and $P_s(L_e + L_s)$, respectively. To simplify the presentation of results, the partial pressures of ethanol in all model compartments were converted to equivalent BAC at 37°C using the following relationship:

$$BAC_{EQ} = \frac{\beta_b}{\beta_g RT} P \quad (6)$$

where R is the universal gas constant (62,360 Torr·cm^3·mol^{-1}·K^{-1}), T is the temperature (K), and β_g and β_b represent solubility (ml ethanol·100 ml medium^{-1}·Torr^{-1}) of ethanol in gas and blood, respectively.

Parameter estimates. We chose parameter values that corresponded to the average dimensions and physical characteristics of healthy skin tissue. The average values and uncertainty ranges for 11 parameters are listed in Table 1. We subjectively chose uncertainty ranges based on the methods used to select the average value. For example, little information is known about $\dot{V}$, but β_b was based on careful measurements. We assigned the former a high level of uncertainty (±50%) and the latter a small level of uncertainty (±10%). We assumed each variable to have a uniform (i.e., rectangular) probability distribution function, where the lower (upper) limit of the probability distribution function corresponded to the average value minus (plus) the uncertainty listed in Table 1. The skin tissue model has dimensions of 1 cm × 1 cm × L, where L is the thickness of each compartment. In our model, the skin tissue is composed of two compartments: the stratum corneum and the epidermis. The thickness of the stratum corneum ranges from 10 to 20 μm (3, 5, 18, 23, 24). On the basis of these data, we chose the thickness of the stratum corneum to be 15 μm (0.0015 cm). The thickness of the epidermis, the distance between the stratum corneum and the center of mass of the capillary vessels, depends on where the blood supply resides. Some investigators state the micro-

Table 1. *Model parameters and uncertainty ranges*

Symbol	Model Parameters	Average Value	Uncertainty, %
β_b	Solubility in blood*	232	± 10
β_e	Solubility in epidermis*	232	± 20
β_s	Solubility in stratum corneum*	211	± 25
D_e	Molecular diffusivity in epidermis, cm^2/s	5.0×10^{-6}	± 25
D_s	Molecular diffusivity in stratum corneum, cm^2/s	5.0×10^{-10}	± 50
L_e	Thickness of epidermis, cm	0.02	± 25
L_s	Thickness of stratum corneum, cm	0.0015	± 25
L_g	Thickness of gas compartment, cm	0.5	± 30
A_c	Capillary surface area, cm^2	7.5×10^{-2}	± 50
$\dot{Q}$	Blood flow, ml/s	4.0×10^{-4}	± 30
$\dot{V}$	Convective gas flow, ml/s	5.0×10^{-5}	± 50

*Units for solubility are ml ethanol·100 ml medium^{-1}·Torr^{-1}.

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