MODELING OF TRANSDERMAL TRANSPORT OF ALCOHOL: EFFECT OF BODY MASS AND GENDER

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ABSTRACT

This paper investigates the effect that body weight and gender have on the transdermal transport of ethanol observed after the ingestion of an alcohol beverage. The approach is to use a computational model which combines a multi-compartment ethanol metabolism model with a transdermal transport model. Males have a larger proportion of alcohol soluble body mass when compared to females of the same weight allowing for greater dilution of the same dose of alcohol, and lower resultant blood alcohol concentrations. In addition, liver size increases with body mass and males have larger livers than females. Examination of these factors has shown that transdermal alcohol concentration lag time is insensitive to body mass and gender because these factors do not significantly affect the alcohol elimination rate.

Keywords: Alcohol, Transdermal, Computational Modeling, Biomedical Modeling

INTRODUCTION

Approximately 17,000 people were killed in alcohol related traffic accidents in 2005; a toll that constituted 39% of all traffic crashes [1]. Preventing drunk driving in the US has proven to be a difficult problem to solve. The fraction of alcohol related fatalities has hovered around 40% over the past 10 years. Due to the lack of progress in reducing alcohol-related traffic fatalities, advanced technologies are being sought to automatically detect intoxicated drivers and disable the vehicle they are attempting to drive [2]. Such technologies exist today in the form of alcohol ignition interlocks which employ a device that automatically checks the driver’s Blood Alcohol Concentration (BAC) using a breath sample before permitting the car to start. However, less invasive methods are desired to encourage widespread usage. One possible way to accomplish this is to use the concentration of alcohol emitted through the skin from the blood stream as a measure of driver intoxication.

After consumption, alcohol is quickly absorbed into the blood stream. The liver eliminates some of the absorbed alcohol from the blood and the heart pumps the rest to all parts of the body including just underneath the surface of the skin. It has been estimated that 0.1% of the total alcohol consumed diffuses from the blood through the skin escaping the body [3]. It has been further shown that the concentration of alcohol escaping the surface of the skin can be related to the concentration of alcohol in the blood. However, the diffusion of alcohol from the blood stream to the surface of the skin is not instantaneous, resulting in a concentration-time profile at the surface of the skin of similar shape to that of the blood’s but lagging behind due to the diffusion delay [4, 5]. If this obstacle could be overcome transdermal sensing of BAC could prove to be a clever method to measure a person’s BAC without collecting a blood or breath sample as current methods require. To better understand the lag between the blood and the skin concentrations an improved version of a computational model developed by the authors to predict the lag time between the peak blood and peak skin alcohol concentrations will be used.

The model used by the authors in previous studies was limited in its ability to differentiate between the lean body mass of males and females [6]. For this study, lean body mass (LBM) will be considered to be the mass of the body that is capable of absorbing alcohol, i.e. the mass of the muscles and other organs that readily absorb alcohol. Adipose tissue and bone are not considered part of the lean body mass because they do not readily absorb alcohol. LBM is an important factor to consider when examining alcohol metabolism because it directly affects the maximum BAC for a given dose of alcohol. If the same amount of alcohol is given to two subjects of the same weight but different LBMs the subject with the larger LMB will have a lower BAC due to a larger available volume of tissue and fluid to dilute the alcohol.

An additional limitation of the previous model was that all subjects were considered to have the same liver size regardless of their total body weight. We assumed that ethanol metabolism only occurs in the liver at a rate proportional the concentration of ethanol in the liver. It is known that liver size varies with body size, however it was not known how liver size variation will affect the blood-skin lag time of the model. Liver sizes scaled to appropriately match body size and gender will be used in this study based on established body-liver size relationships.

This study will examine how gender and variations in liver size affect the lag time between the blood and skin alcohol concentrations using an improved model that scales LBM and liver mass to better represent males and females of different body masses.

METHODS

To model the metabolism and transport of alcohol through the skin, two coupled computational models were developed. A compartmental model was used to predict the metabolism of a single dose of alcohol given in solution and a one dimensional diffusion model was used to predict the concentration of alcohol at the surface of the skin based on the concentration of alcohol in the blood.

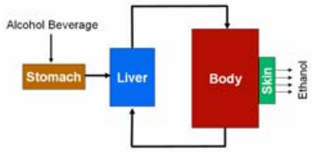

Figure 1. Model Diagram

After oral consumption, an alcoholic beverage enters the stomach. The stomach empties into the small intestine where the alcohol is quickly absorbed into the blood stream. The alcohol absorbed into the blood by the small intestine next enters the liver through the Portal vein where some of the alcohol is metabolized. The alcohol that is not metabolized on its first pass through the liver continues to circulate in the blood stream eventually diffusing into the lean body mass. Repeated circulation of the blood containing alcohol through the liver eventually results in the elimination of all alcohol.

To model this process a three compartment model was used as shown in Figure 1. The stomach compartment accepts an initial dose of alcohol diluted in solution. The stomach empties at a rate proportional to its current volume using relationships experimentally determined by Umulis et al [7]. To simplify the model, the stomach compartment empties directly into the liver, skipping the small intestines. This assumption is reasonable because no alcohol is metabolized in the small intestine before it enters the liver via the Portal vein; the lag time between stomach and liver is accounted for in the stomach empty rate. The change in alcohol concentration over time in the liver is described by Equation 1. The term $k_s V_{Stomach} C_{Stomach}$ represents the stomach emptying rate, or the rate that alcohol is added to the liver in mole/minute. It is assumed that alcohol elimination only occurs in the liver at a rate determined by the current concentration limited by the term V_{max} following Michaelis – Menten kinetics for enzymatic reactions represented by the last term in Equation 1. The amount of alcohol moving out of the liver and into the LBM is governed by the difference in their respective alcohol concentrations at a rate controlled by the blood flow rate, Q.

$$V_{Liver}\frac{dC_{Liver}}{dt} = Q\left(C_{LBM} - C_{Liver}\right) + \left(k_s V_{Stomach} C_{Stomach}\right) - \frac{V_{max} C_{Liver}}{K_m + C_{Liver}} \tag{1}$$

Equation 2 describes the change in alcohol concentration in the LBM based on the concentration of alcohol in the liver at a rate governed by the blood flow rate, Q.

$$V_{LBM}\frac{dC_{LBM}}{dt} = Q\left(C_{Liver} - C_{LBM}\right) \tag{2}$$

The metabolism model determines how the concentration of alcohol in the blood changes with time after an initial dose given in solution for a given LBM and liver size. The blood alcohol curve is then used to drive the coupled skin diffusion model. The alcohol in the blood stream has to diffuse through the epidermis and stratum corneum in order to escape the body as depicted in Figure 2. To model this phenomenon a four layer system was used consisting of the blood, epidermis, stratum corneum, and outside air. The blood boundary concentration is driven by the body alcohol concentration from the metabolism model and the air boundary has a constant alcohol concentration of 0, thus setting up a concentration gradient.

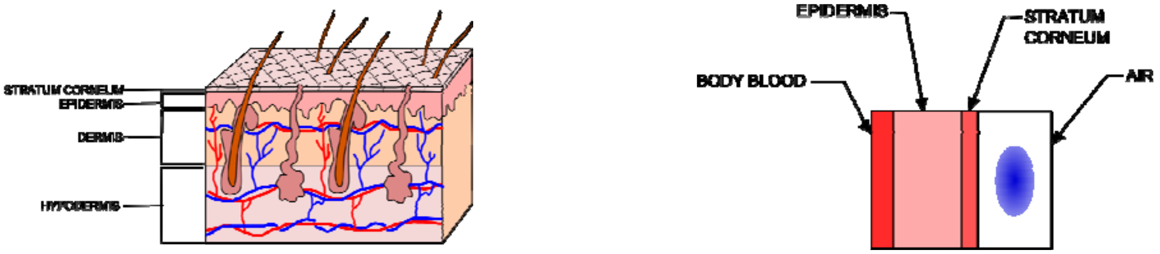

Figure 2. (a) Skin Diagram (Adapted from [8]) (b) Skin Model

Equation 3 describes the change in partial pressure of alcohol in the epidermis, P_e, both spatially and temporally. Similarly, Equation 4 governs the change in partial pressure of alcohol in the stratum corneum, P_s, spatially and temporally.

$$\frac{\partial P_e}{\partial t} = D_e \frac{\partial^2 P_e}{\partial x^2} \qquad 0 \le x < L_e \tag{3}$$

$$\frac{\partial P_s}{\partial t} = D_s \frac{\partial^2 P_s}{\partial x^2} \qquad L_e < x \le L_e + L_s \tag{4}$$

For Equations 3 and 4 D_e is the molecular diffusivity, L_e is the thickness of the epidermis, D_s is the molecular diffusivity and L_s is the thickness of the stratum corneum. These values were given by Anderson [9].

To examine the effect of gender and scaled liver size on the transdermal transport lag of alcohol 5th, 50th and 95th percentile body weights based on the US population will be used [10]. It will be assumed that the lean body mass of males is 68% of their total body mass and 55% for females [11]. Liver weight was calculated based on the relationship between body mass and gender developed by Chan et al [12]. A summary of the values used in this analysis is given in Table 1.

Table 1. Summary of Model Input Variables

	Weight Percentile					
	5th		50th		95th	
	Male	Female	Male	Female	Male	Female
Body Mass (kg)	60.4	49.8	83.5	70.2	121.2	110.2
Lean Body Mass (kg)	41.1	27.4	56.8	38.6	82.4	60.6
Liver Weight (kg)	1.0	0.8	1.3	1.1	1.8	1.6

The metabolism model and transdermal transport model were solved using MATLAB. A stiff ordinary differential equation solver was used for the metabolism model and a forward finite difference approximation was used to solve the skin diffusion model.

RESULTS

The coupled model was validated using available published results from an experiment testing a transdermal alcohol sensor [5]. The subject was assumed to be a 50th percentile male and was given 0.75 ml of 95% ethanol per kg of body weight diluted 4:1 in cold orange juice. These parameters were used to generate the plots given in Figure 3.

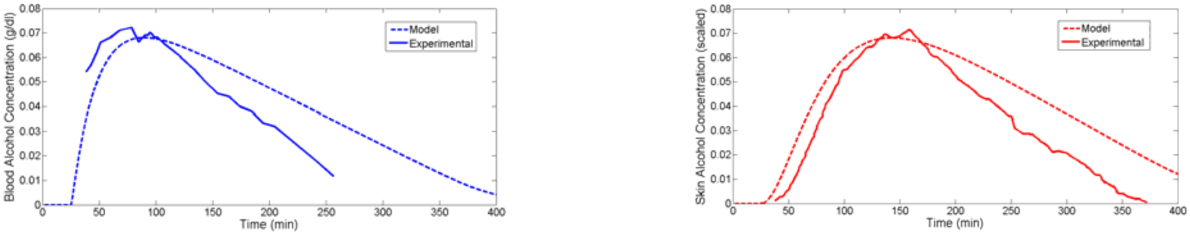

Figure 3. Model Validation with Experimental Data (a) Blood Alcohol Concentration (b) Skin Alcohol Concentration

Simulations were run using the values given in Table 1 for 15, 30, 45 and 60 ml doses of 95% alcohol diluted in 150 ml of solution.

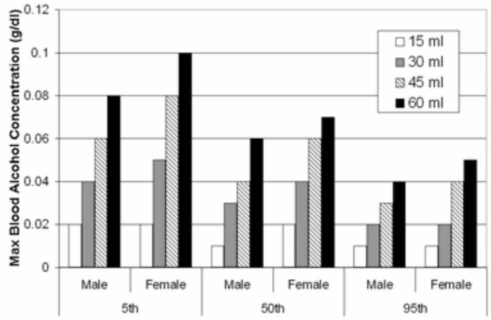

Figure 4. Max BAC

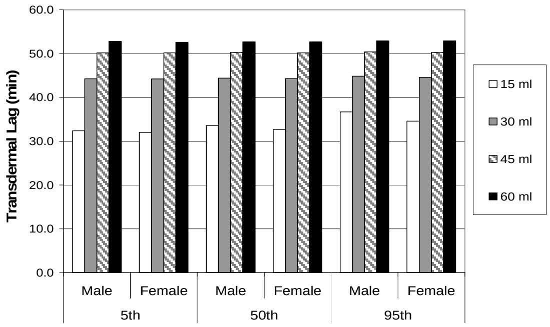

Figure 5. Transdermal Lag

Figure 4 shows maximum blood alcohol concentration as a function of gender, weight percentile and alcohol dose. Figure 5 shows the blood-skin peak alcohol concentration lag as function of gender, body weight and alcohol dose. Figure 6 is a plot of the transfer rate of alcohol into the liver from the stomach and body as well as the alcohol elimination rate.

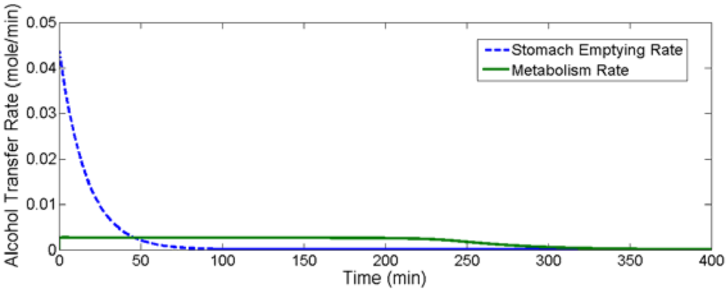

Figure 6. Transport and Elimination Rates in the Liver

DISCUSSION

Model Validation

The model validation plot shown in Figure 3 shows that the model curves track the experimental data closely for both the blood and skin alcohol concentrations. The experimental data used to validate the model expressed the skin alcohol concentration in terms of the electrical current output from the instrument used to gather the data. For this reason the model can only be used to study the peak time lag between the blood and skin and not the magnitude of the skin alcohol concentration.

Effect of Gender of Transdermal Lag

The variations in male and female LBM were incorporated into the model effectively reducing the amount of alcohol soluble body mass available to dilute ingested alcohol in females when compared to a male of the same body weight. In addition, males were modeled to have larger livers than females of the same body weight; effectively increasing the concentration of alcohol in the liver for females when compared to males of the same weight. Examination of Figure 4 shows that females will have higher maximum BACs after consumption of the same dose as males in the same weight percentile. Inspection of Figure 5 shows that transdermal concentration lag is insensitive to gender. For a given dose and body mass both genders had approximately the same lag time. Only at low doses of alcohol does variance in lag time within a gender/weight group become apparent.

Effect of Body Weight and Liver Scaling on Transdermal Lag

Figure 4 shows that as body weight increases the maximum observed BAC decreases for a given dose of alcohol. An increase in body weight increases LBM with respect to gender allowing alcohol to be diluted to a greater extent in a larger person than in a small person. This results in a decrease in max BAC. Figure 5 shows that for a given dose of alcohol, transdermal lag is body weight insensitive. The blood-skin peak lag time for all body weights for a given dose of alcohol were approximately the same.

Effect of Body Weight, Lean Body Mass and Liver Size on Metabolism Time

Scaling the liver and LBM size has little effect on alcohol metabolic rate. This is best explained in Figure 6 which shows mass flow rates of alcohol into the liver. The size of the liver directly affects the concentration; larger livers will have lower alcohol concentrations when compared to smaller livers for the same dose. Alcohol elimination rate is governed by the concentration of alcohol in the liver but limited by V_{max}. The ‘Metabolism Rate’ curve in Figure 6 quickly reaches a plateau equal to the value of

V_{max} and remains at this level for most of the simulation. For all simulations the alcohol metabolism rate quickly reaches V_{max}. Changes in the liver size only affect the alcohol metabolism rate at the end of the simulations when the concentration in the liver drops low enough to not overwhelm the K_m term of Equation 1. Men and women of all weights reach their maximum and minimum peak BACs at nearly the same time for a given dose of alcohol explaining why body weight and gender have no effect metabolism time or blood-skin lag.

Limitations

The model was validated using data from a 50th percentile male given a single does of alcohol; therefore the results may not be applicable for other body weights or genders. All subjects were taken to have the same maximum metabolic rate, stomach empting constant and skin diffusion coefficient which may not accurately represent the actual population. In addition, the model does not reduce amount of alcohol in the body by the amount predicted to leave the skin. The model also does not account for alcohol lost through the breath, estimated to be 0.7% of the total dose, or alcohol excreted in the urine, estimated to be 0.3% of the total dose [3]. Since such small fractions of alcohol are lost through the breath and urine, they were not included as elimination paths in the model; however their absence may explain why the experimental data shows a faster elimination rate when compared to the model after the curve peaks.

CONCLUSIONS

This study examined how gender and body weight affect blood-skin concentration lag in humans after oral ingestion of alcohol using an improved validated computation model. It was found that body mass and gender do not significantly affect the time lag between peak blood and skin alcohol concentrations. This is because body mass and gender do not significantly affect metabolic time resulting in similar BAC peak times. When applied to the skin diffusion model, virtually no change in peak lag was noted.

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