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ORIGINAL ARTICLE

A regression model applied to gender-specific ethanol elimination rates from blood and breath measurements in non-alcoholics

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Abstract As elimination rates for alcohol are suggested to be gender specific, a novel regression model has been applied to estimate these rates for both men and women using experimentally measured data from 81 female and 96 male volunteers described in previous papers. Breath alcohol measurements were done with the Alcotest 7110 Evidential device and were coupled with concomitant sampling of venous blood. Statistical analyses involved use of a mixed linear model for blood alcohol concentration (BAC) and breath alcohol concentration (BrAC), respectively. The model takes regression lines for each test subject into account with an individual starting value (2 h after the end of drinking) and with an individual alcohol elimination rate per hour (coincidental effects). Further, the data was modeled so that an average alcohol elimination rate per hour could be estimated separately for both genders (constant effects). This enables us to methodically correctly estimate the back calculation. The elimination rates β_{60}, which can be used for minimum and maximum back calculations for the BAC, were 0.115 g/kg/h and 0.260 g/kg/h, respectively, for women and 0.096 g/kg/h and 0.241 g/kg/h, respectively, for men. These figures widely deviate from gender-unspecific values commonly used in Germany (0.1 and 0.2 g/kg/h, respectively). The corresponding values for the BrAC were 0.061 mg/l/h and 0.124 mg/l/h for women and 0.049 mg/l/h and 0.112 mg/l/h for men. The probability of an over- or underestimation of the abovementioned extreme values is 0.3% in each case.

Keywords Breath alcohol concentration · Blood alcohol concentration · Regression analysis · Back calculations

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Introduction

Today, adequately precise measuring devices are available for the determination of breath alcohol levels. The rate of elimination in breath is 0.07 mg/l/h on average [14, 18]. Since the 1980s, it has been discussed that women are able to eliminate alcohol significantly faster than men and the causes for this phenomenon have been intensely disputed [2, 5, 17, 23, 26–28].

The average ethanol elimination rates from blood of 0.14 g/kg/h to 0.16 g/kg/h are considered to be less important than the so-called extreme values [32]. If the concentration measured at the time of examination of a defendant is used to calculate back to the time a crime was committed, the basic law of ‘in dubio pro reo’ prevents the defendant from being subjected to a rate of back calculation that is either too high (i.e., traffic law) or too low (i.e., in the appraisal of criminal responsibility). According to the

Table 1 Description of the study population and number of measurements according to gender

	Women (n=81)	Men (n=96)
Weight (kg) mean±SD (min; max)	62.6±10.7 (46; 118)	78.7±13.1 (56; 131)
BMI (kg/m^2) mean±SD (min; max)	22.3±3.5 (16.7; 40.4)	23.6±3.2 (18.5; 37.1)
Max. BAC (g/kg) mean±SD (min; max)	0.87±0.20 (0.42; 1.38)	0.89±0.17 (0.52; 1.31)
BAC measurements (in total)		
Per subject	12–32	12–34
Median	20	19
Total	1,598	1,969
BAC measurements[a] (linear phase)		
Per subject	2–14	3–14
Median	5	6
Total	457	608
Max. BrAC (mg/l) mean±SD (min; max)	0.44±0.09 (0.23; 0.67)	0.46±0.08 (0.26; 0.66)
BrAC measurements		
Per subject	12–32	12–33
Median	19	20
Total	1,597	1,955
BrAC measurements[a] (linear phase)		
Per subject	2–13	2–12
Median	4	5
Total	387	546

SD standard deviation, *BMI* body mass index, *min* minimum value, *max* maximum value

[a] Measurements at $t \geq 2$ h after the end of drinking used for regression analysis

German legislation, a minimum (0.10 g/kg/h) or maximum (0.20 g/kg/h) elimination rate must be assigned, for which general agreement exists. These values are based on the calculations by Freudenberg in his report for the Federal public health department, for which the probability that these values will be exceeded is 0.3% in each case [11]. Comparable extreme values for the back calculation of breath alcohol measurements have not yet been established. The aim of this study was to determine the minimum and maximum values for the elimination rates via statistical calculations for BAC and breath alcohol concentration (BrAC) for both genders separately.

Materials and methods

Drinking experiments and methods used for determination of venous blood and breath alcohol concentrations were previously described [8, 9] together with the data from 81 female and 96 male volunteers statistically evaluated in the present study.

The statistical analysis was performed using a mixed linear model [31], separately for BAC and BrAC. The model takes the regression lines for each test subject into account, including an individual starting value (2 h after the end of drinking) and an individual rate of elimination of alcohol per hour (coincidental effects). Further, the data were modeled so that the average disappearance per hour was estimated separately for both genders (constant effects). This procedure allows for a methodically correct estimation of the back calculations. The statistical prerequisites for the model were verified and were indeed fulfilled. The equation of the mixed linear regression model is shown below:

$$Y_{ij} = \mu + \mu_i + \beta t_{ij} + \beta_i t_{ij} + \gamma x_i t_{ij} + e_{ij}$$

Y_{ij} is the alcohol concentration (BAC or BrAC) of the i-th test subject at time j, $(\mu+\mu_i)$ is the alcohol concentration of the i-th test subject at time 0, whereby μ_i with $\mu_i \sim N(0, \sigma_m{}^2)$ is assumed to have a normal distribution. The covariable t_{ij} describes the time of the j-th measurement of the i-th test subject, and the covariable x_i (0 or 1) describes the gender. The variables that are most important for the elimination rates are the slope parameters β, β_i and γ. β describes the average elimination rate for women and $(\beta+\gamma)$ corresponds to that of men. The elimination rate for the i-th woman is $(\beta+\beta_i)$ and for the i-th man is $(\beta+\beta_i+\gamma)$, where β_i represents the deviation of the i-th test subject from the corresponding average value in the elimination rate; $\beta_i \sim N(0, \sigma_t{}^2)$ is assumed to have a normal distribution. e_{ij} represents the residual with $e_{ij} \sim N(0, \sigma^2)$.

The estimation of $(\mu+\mu_i)$ itself is not of interest; it merely represents the theoretical alcohol concentration at the beginning of the experiment based on a linear extrapolation. However, there are numerous parameters in the statistical model which allow for individual starting values for each subject.

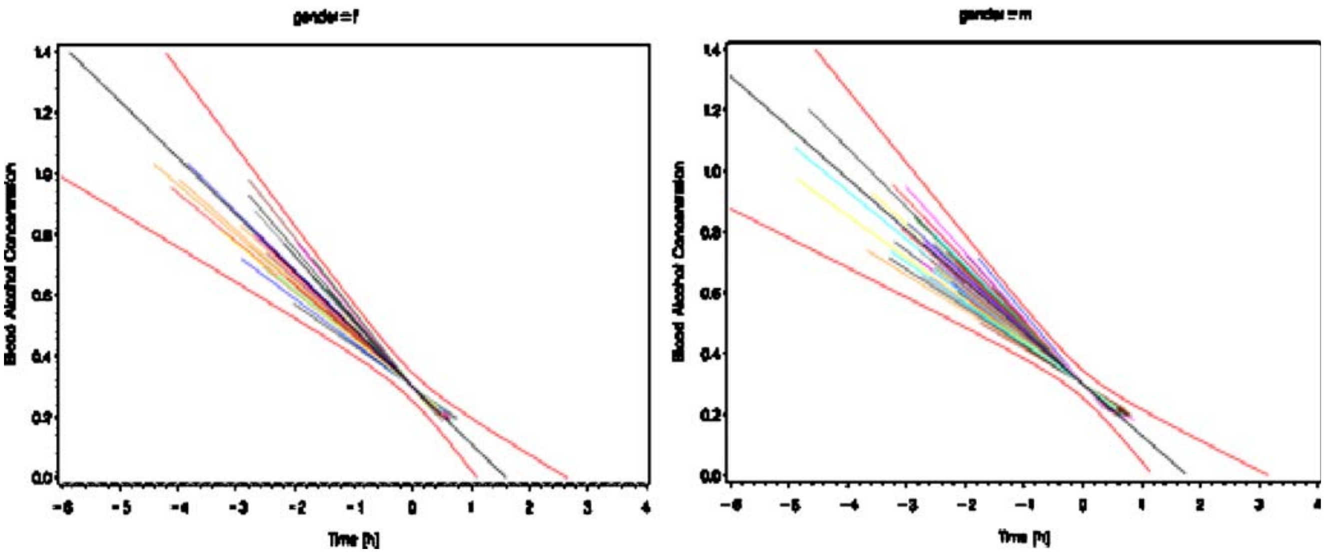

Fig. 1 **a** Variation of the elimination rates for women. **b** Variation of the elimination rates for men. Time t=0 h represents the time when back calculation starts. The *outer lines* indicate the lower and upper limit of the reference interval, which provides the minimum and maximum back calculation values

Extrapolating back to the time t=0 when back calculation starts gives θ_0 for each individual. Thus, by substituting θ_0 into the model equation (plug-in method) for the value ($\mu+\mu_i$), the backward projection Z at time t can be calculated by:

$$Z(t) = \theta_0 + \beta t + \gamma x_i t$$

Based on the standard deviation calculations it is only possible to specify one $(1-\alpha)$ reference interval at time t (RI(t)). With a probability of $(1-\alpha)$, the alcohol concentration at time t fell within this interval. Only measurements with $t \geq 2$ h after the end of drinking were taken in order to be sure that alcohol concentration has started to decrease.

$$\begin{aligned}\alpha)\mathrm{RI(t)} &= Z(t) \pm z_{1-\alpha/2}\mathrm{SD(Z(t))}\\ &= Z(t) \pm z_{1-\sigma/2}\,\mathrm{sqrt}\left(\mathrm{t}^2\sigma t_t^2 + \sigma^2\right)\end{aligned}$$

where $z_{1-\alpha/2}$ is the $1-\alpha/2$ quantile of the standard normal distribution. In accordance with Freudenberg, the calculation of the minimum and maximum degree of the confidence interval came to 99.4% (α=0.006), which corresponds to 99.7% using a one-tailed test of significance. The lower and upper limits of the reference interval provide the minimum and maximum back calculation values. Based on the small quadratic influence, the asymptote was additionally calculated with an empirical formula and is also presented.

The statistical analyses were performed with Statistical Analysis System Version 8 (SAS Institute Inc. Cary, NC, USA).

Results

A description of the study population (weight, BMI, maximum BAC, and BrAC measurements) is given in Table 1 as partially presented in previous publications [8, 9].

Also, 1,065 BAC and 933 BrAC measurements could be used for regression calculations (Table 1). In order to better compare individual regression lines, they were bundled via displacement parallel to the x-axis. The reference intervals (minimum or lower limit for the back calculation as well as maximum or upper limit for the back calculation) are shown in Fig. 1 (a and b), separated by gender. The individual elimination rates based on BAC as estimated by the regression model were between 0.134–0.248 g/kg/h for women and 0.115–0.232 g/kg/h for men. The elimination rates for the BrAC ranged from 0.069 to 0.114 mg/l/h for women and from 0.053 to 0.105 mg/l/h for men (Table 2).

The average hourly elimination rate β_{60} of the BAC in women was 0.187 g/kg/h (95% confidence interval of

Table 2 Average, minimum, and maximum elimination rates in women and men

	Women (n=81)	Men (n=96)
Blood alcohol (g/kg/h)		
Average elimination rate β_{60}	0.187	0.169
Minimum elimination rate	0.115	0.096
Maximum elimination rate	0.260	0.241
Breath alcohol (mg/l/h)		
Average elimination rate β_{60}	0.092	0.080
Minimum elimination rate	0.061	0.049
Maximum elimination rate	0.124	0.112

Table 3 Back calculation formulas

Parameter Gender	Back calculation formulas
BAC	Upper and lower reference limits
Women[a]	θ_0+0.187 t±2.748 sqrt(t^2 0.000690+0.000274)
Men[a]	θ_0+0.169 t±2.748 sqrt(t^2 0.000690+0.000274)
BAC empirical formula	Empirical formula
Women	θ_0+0.115 t resp. θ_0±0.260 t
Men	θ_0+0.096 t resp. θ_0±0.24 t
BrAC	Upper and lower reference limits
Women[a]	θ_0+0.092 t±2.748 sqrt(t^2 0.000132+0.000041)
Men[a]	θ_0+0.080 t±2.748 sqrt(t^2 0.000132+0.000041)
BrAC empirical formula	Empirical formula
Women	θ_0+0.061 t resp. θ_0+0.124 t
Men	θ_0+0.049 t resp. θ_0+0.112 t

[a] The lower limit of the two-sided 99.4% reference interval is designated with a "–" and the upper limit is designated with a "+". θ_0 is the measurement at time t=0 when back calculation starts

0.181–0.194), and in men it was 0.169 g/kg/h (95% confidence interval of 0.163–0.174). The difference between the sexes of 0.0185 g/kg/h (0.010–0.027) was statistically significant (p<0.0001).

The average elimination rate, β_{60}, for BrAC was 0.092 mg/l/h in women with a 95% confidence interval of 0.089–0.095 and 0.080 mg/l/h (0.078–0.083) for men (Table 2). The difference between the sexes of 0.012 g/kg/h (0.008–0.016) was statistically significant (p<0.0001).

The back calculation formulas with the upper and lower reference limits are shown in Table 3. The quadratic term in the formula for the reference interval is very small and thus this empirical formula is very exact. Figure 1 reflects the influence of the quadratic term. Applying the formula to a starting BAC value of θ_0=0.3 g/kg and a 2-h backward projection, e.g., the following lower/upper limits can be assessed: 0.523 g/kg/0.826 g/kg for women and 0.486 g/kg/0.789 g/kg for men, respectively. The results obtained from the empirical formula are very similar (Table 4).

Discussion

The basis of the back calculations used in forensic cases in Germany today stems from Freudenberg from 1966 [11]. In his report, the minimal rate of elimination of ethanol was determined to be 0.10 g/kg/h. The formula used included 99.4% of cases, which corresponds to a 0.3% probability of an overestimate. The maximum elimination rate was determined to be 0.20 g/kg/h using an equation of the same kind.

The present elimination rates were analyzed in accordance with Freudenberg (1966) under the same hypothesis using a novel mixed linear regression model. Although a probability of 0.3% was chosen for the outer limits of the frequency distribution. Freudenberg's results could only be partially confirmed.

Being mostly from male subjects, Freudenberg's results can be compared with our group of male test subjects only [11]. The back calculations obtained from this study are not linear as in Freudenberg's work, but rather slightly quadratic. The asymptote values can, however, be used for reasons of comparison, as the empirical formula is linear. These were 0.096 g/kg/h and 0.241 g/kg/h for males instead of an elimination rate of 0.1 and 0.2 g/kg/h. The lower limit of the distribution curve was thus verified, whereas the upper limit was much higher. This finding can probably be explained through social changes in drinking habits over the past 40–50 years, both in frequency and amount [10]. This increase in consumption can lead to elevated elimination rates via induction of the MEOS [21], as can be observed in its extreme form in alcoholics [13, 15].

A comparison with our female subjects is not possible. The recent finding that women eliminate alcohol more quickly than men could again be confirmed [1, 3–7, 12, 16, 17, 19, 20, 22, 23–25, 28–30]. The frequency distribution of β_{60} in women was nearly identical to that in men, except that both the averages as well as the extreme values were roughly 0.019 g/kg/h and 0.012 mg/l/h higher, respectively. In order to achieve the same confidence level as in men, BAC backward projections should be set at 0.115 g/kg/h and 0.260 g/kg/h for women.

Table 4 Examples of back calculation for a starting value θ_0=0.3 g/kg and a back-projection time of 2 h using the equations of Table 3

	Women	Men
BAC (g/kg);		
Back calculation (expected)	0.675	0.637
Back calculation (reference limits)	0.523; 0.826	0.486; 0.789
Back calculation (empirical formula)	0.530; 0.819	0.493; 0.782
BrAC (mg/l); initial value θ_0=0.15 mg/l		
Back calculation (expected)	0.334	0.310
Back calculation (reference limits)	0.269; 0.400	0.245; 0.376
Back calculation (empirical formula)	0.271; 0.397	0.247; 0.373

Although there is no obvious explanation for the gender-dependent elimination rate, the identical form of the frequency distribution counters the idea that several and, in addition, variable factors play a role, as one would expect a one-tailed deviation rather than a parallel shift if that is the case. For an estimation of the range, however, this is relatively unimportant as back calculations must take all conceivable influences into account.

The back calculation limits based on breath alcohol measurements have not yet been established in Germany. The requirements for a quasi-linear curve in the post-absorptive elimination phase for concentrations >0.10 mg/kg can, however, be considered as fulfilled [7, 14, 16]. In addition, gender-specific differences should be taken into account. If the same standards for the probability are kept as for the BAC back calculations, values of 0.061–0.124 mg/l/h for women and 0.049–0.112 mg/l/h for men would apply.

Although 177 volunteers participated in this study, definite reference ranges should be based on a larger population in which the variation might be slightly different.

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