Revised equations allowing the estimation of the uncertainty associated with the Total Body Water version of the Widmark equation

Peter D Maskell[a*] and Ann-Sophie Korb[a,b]

[a]Forensic Medicine and Science, University of Glasgow, University Avenue, Glasgow G12 8QQ, UK

[b]School of Computing, Engineering and Physical Sciences, University of West Scotland, Paisley Campus, Paisley. PA1 2BE, UK

*Corresponding Author: peter.maskell@glasgow.ac.uk

DOI: 10.1111/1556-4029.14859

ABSTRACT

Widmark calculations are the most commonly used alcohol calculations to estimate a) the amount of alcohol consumed based on blood alcohol concentration (BAC) and b) blood alcohol concentrations at a set time after consumption of a known amount of alcohol. These calculations are vital forensic casework. Previous work has demonstrated that using general error propagation-based equations the variability associated with alcohol calculations can be estimated but these equations have only been determined for the volume of distribution version of the Widmark equation. However, recent investigations have shown that the total body water (TBW) version of the Widmark equation is more reliable than the version that utilises the apparent volume of distribution of ethanol. To date there is no general error propagation equation to determine the variability associated the TBW version of the Widmark equation. Using previously published studies of 185 individuals in which alcohol elimination rate (β) and ethanol's volume of distribution were determined we have shown that there is a negative correlation (-0.247) between the alcohol elimination rate (β) and TBW. Using these data, we were able to produce equations allowing the estimation of the variability of the results calculated using the TBW version of the Widmark equation. This will allow forensic practitioners to give the best determination of the variability associated with Widmark calculations currently possible.

KEYWORDS

Widmark; Alcohol calculations; variability; Total body water; Blood alcohol; Alcohol elimination rate

HIGHLIGHTS

- Widmark calculations are the most commonly use alcohol calculations
- General error propagation equations allow estimation of variability with these calculations
- This work demonstrates the correlation between alcohol elimination and total body water
- This correlation allows estimation of the variability with total body water containing Widmark calculations

The most common equation used for forensic purposes to model the pharmacokinetics of ethanol is the Widmark equation named after Eric Widmark and his pioneering work in the early 20th century (1). There are two versions of his equation, one that uses the volume of distribution of ethanol (r) and one that utilises the total body water (TBW) of an individual:

$$C_o = \frac{100.v.z.d}{r.M} \; or \; \frac{100.v.z.d.F_{water}}{TBW} \qquad (1)$$

C_o - the hypothetical BAC at zero time before any metabolism has occurred (mg/100mL)

v – Volume of alcoholic beverage consumed (mL)

z – Strength of alcoholic beverage (%v/v)

d – Density of ethanol (0.789 g/mL)

r – Volume of distribution of ethanol (L/kg)

M – Body mass of the individual (kg)

F_{water} –fraction of blood volume that is water (on average in women this is 0.838 %w/v and 0.825 %w/v in men).

TBW - an individual's total body water (L)

The blood alcohol concentration after a known time (t) can then be determined from the following equation:

$$C_t = C_o - \beta.t \qquad (2)$$

C_t = blood alcohol (ethanol) concentration at time t (mg/100mL)

β = alcohol elimination rate (mg/100mL/h)

t = duration of the drinking session (h)

Transformation of the Widmark equation(s) also allow an estimation of the volume of an alcoholic beverage consumed to be determined. Again, there are two versions of the equation one based on r and the other on TBW.

$$v = (C_B + \beta t) \times \frac{r.M}{100.z.d} \; or \; (C_B + \beta t) \times \frac{TBW}{100.z.d.F_{water}} \tag{3}$$

C_B = Analytically determined blood alcohol concentration (mg/100mL)

With all of these calculations it is important to take into account the variability that is inherent in these calculations. The variability of these equations were recognised by Widmark (1) and Alba (2) but were not fully explored until the work of Gulberg (3), Searle (4) and Maskell and Cooper (5). The general error propagation equation used to estimate the variability of the results of the calculations involving r for blood alcohol concentration at time t (C_t) is:

$$e_{C_t} = \frac{C_o}{C_t}\sqrt{[e_v^2 + e_d^2 + e_z^2 + e_r^2 + e_M^2] + \left(\frac{\beta t}{C_o}\right)^2 [e_\beta^2 + e_t^2] - 1.3\left(\frac{\beta t}{C_o}\right) e_r e_\beta} \tag{4}$$

and for the volume of the alcohol beverage consumed (v):

$$e_v = \sqrt{\left[\frac{C_B}{C_o}\right]^2 e_B^2 + \left[\frac{\beta t}{C_o}\right]^2 (e_\beta^2 + e_t^2) + (e_r^2 + e_d^2 + e_z^2 + e_M^2) - 1.3\left[\frac{\beta t}{C_o}\right] e_r e_\beta} \tag{5}$$

e_{ct} = coefficient of variance of the calculated blood alcohol concentration

e_v = coefficient of variance of the volume of drink consumed

e_d = coefficient of variance of density of alcohol (ethanol)

e_z = coefficient of variance of the alcoholic strength of the drink consumed

e_r = coefficient of variance of volume of distribution of ethanol of the subject

e_M = coefficient of variance of the mass of the subject

e_β = coefficient of variance of alcohol elimination rate

e_t = coefficient of variance of the duration of the drinking session

e_B = coefficient of variance of the blood alcohol analysis result

Recent work has demonstrated the TBW version of the Widmark equation has been determined to be more reliable and gives lower variability when compared to the r version (6). However, to date, there are no general error propagation equations to allow the estimation of the variability associated with the TBW version of the Widmark equation. Studies in the mid-20th century demonstrated that there is a correlation between the volume of distribution of ethanol (r) and the elimination rate of ethanol (β) (7), knowledge of the value of this correlation is required to allow the calculation of the variability of the TBW version of Widmark calculations. In this study we use previously published studies to determine the correlation (if any) between TBW and β allowing the production of the general error propagation variability equation for the TBW version of the Widmark equation.

Materials and Methods

From a search of the literature 5 publications were identified in which both the volume of distribution of ethanol and the elimination rate for each individual was determined. The studies all gave a bolus dose alcohol on an empty stomach giving a bioavailability as close as possible to 100% the gold standard methodology for alcohol studies (8–12). 4 out of the 5 studies identified provided β, r, and TBW values for both males and females, where the study by Freudenberg and Mallach (8) provided overall values of β, r, and TBW for their subjects without making such a discrimination. No studies were identified in the literature where both total body water and the elimination rate of alcohol had been determined. Using equation 6 and the F_{water} (males (0.825 %w/v (5)); females (0.838 %w/v (5)) and a mean F_{water} (0.832 %w/v) in the study where the sex of the individuals was not given (8)) it is possible to convert r to TBW:

$$TBW = M \times F_{Water} \times r \quad (6)$$

In a number of the studies the alcohol concentration was given in mg/g rather than the now more commonly used mg/100mL. The average density of blood (1.055 g/mL (13)) was used to covert blood alcohol concentrations to mg/100mL. The published data was compiled using

Microsoft Excel 2013. Data analysis was carried out using GraphPad Prism V6.01. The correlation between TBW or r and β was determined using Pearson's correlation coefficient. An $\alpha \leq 0.05$ was considered significant.

Results and Discussion

The mean (± SD) of the alcohol elimination rate (β), ethanol volume of distribution (r) and total body water (TBW) of the 184 individuals in the various studies can be found in Table 1. The mean β 14.7 ± 3.2 mg/100mL/h was lower than the currently accepted mean of 19.1 mg/100mL/h (7) for ethanol elimination, however as the studies in table 1 were completed in the mid to late 20th century this is likely to reflect the changes in drinking patterns in the last 50 years. The mean r for males and females in this study were 0.72 ± 0.10 L/kg; n = 76 and 0.65 ± 0.08 L/kg; n = 53 respectively compared to 0.69 ± 0.09 L/kg; n = 173 (males) and 0.60 ± 0.10 L/kg; n = 63 (females) in a previous large scale study (14) although this is likely to reflect slight variation in the subjects in the studies. These data allow β and TBW or r to be plotted to determine the correlation, if any, between β and TBW or r.

As can be seen in figure 1 the combined data of the 5 studies was used to plot the relationship a) β vs r and b) β vs TBW. As with previous studies (7,15) a negative correlation (-0.452) was found between β vs r ($p<0.001$) and this study also demonstrates there is a negative correlation between β vs TBW (-0.247; $p<0.0001$). This correlation value allows the determination of the general error propagation equation for variability for TBW based Widmark equations.

For determination of the blood alcohol concentration at time t:

$$e_{C_t} = \frac{C_o}{C_t}\sqrt{\left[{e_v}^2 + {e_d}^2 + {e_z}^2 + {e_{TBW}}^2 + {e_{F_{water}}}^2\right] + \left[\frac{\beta t}{C_o}\right]^2 \left[{e_\beta}^2 + {e_t}^2\right] - 0.494\left[\frac{\beta t}{C_o}\right] e_{TBW} e_\beta} \qquad (7)$$

And the determination of the volume of an alcoholic beverage consumed

$$e_v = \sqrt{\left[\frac{C_B}{C_o}\right]^2 {e_B}^2 + \left[\frac{\beta t}{C_o}\right]^2 \left({e_\beta}^2 + {e_t}^2\right) + \left({e_{TBW}}^2 + {e_d}^2 + {e_z}^2 + {e_{F_{water}}}^2\right) - 0.494\left[\frac{\beta t}{C_o}\right] e_{TBW} e_\beta} \qquad (8)$$

e_{TBW} = coefficient of variance of the total body water of the subject

e_{Fwater} = coefficient of variance of fraction of blood volume that is water

Previous work has determined the variance for each of the terms associated with the TBW variability equations (7) and (8) and these are detailed in table 2. A spreadsheet that allows the calculation of the variability of Widmark calculation estimates is included as supplementary material (S1).

Limitations of the Study

The data used in this study is limited as ideally a study would be carried out using a wide variety of individuals of varying sex, race and body size. The study would directly measure the TBW of the individual using tritium dilution and then in the same individual the elimination rate of ethanol would be determined. However, this study gives the best correlation between β and TBW to date and is suitable for forensic use.

Conclusions

This study allows forensic practitioners to determine the variability associated with the most reliable version of the Widmark calculation that containing TBW. In order to help forensic practitioners an excel spreadsheet is available as supplementary material allowing the calculation of variability associated with TBW.

References

1. Widmark EMP. Principles and applications of medicolegal alcohol determinations. Biomedical Publications, Davis. CA., 1981. p163

2. Alha A. Blood alcohol and clinical inebriation in Finnish men. Ann Acad Sci Fenn A 1951;26:1-136.

3. Gullberg RG. Estimating the uncertainty associated with Widmark's equation as commonly applied in forensic toxicology. Forensic Sci Int 2007;172(1):33–9. https://doi.org/10.1016/j.forsciint.2006.11.010.

4. Searle J. Alcohol calculations and their uncertainty. Med Sci Law 2015;55(1):58–64. https://doi.org/10.1177/0025802414524385.

5. Maskell PD, Cooper GAA. Uncertainty in Widmark equation calculations: Volume of distribution and body mass. J Forensic Sci 2020;65(5):1676–84. https://doi.org/10.1111/1556-4029.14447.

6. Maskell PD, Jones AW, Heymsfield SB, Shapses S, Johnston A. Total body water is the preferred method to use in forensic blood-alcohol calculations rather than ethanol's volume of distribution. Forensic Sci Int 2020;316:110532. https://doi.org/10.1016/j.forsciint.2020.110532.

7. Jones AW. Evidence-based survey of the elimination rates of ethanol from blood with applications in forensic casework. Forensic Sci Int 2010;200(1–3):1–20. https://doi.org/10.1016/j.forsciint.2010.02.021.

8. Freudenberg K, Mallach HJ. Remarks on the constants Co and r by Widmark. Blutalkohol 1966;3(7):372–80.

9. Springer E. On the path of blood alcohol curves after wine consumption. Blutalkohol 1971;8:84–94.

10. Mallach HJ. On the path of blood alcohol curves after beer consumption. Blutalkohol 1966;3(7):308-319.

11. Osterlind SM, Ahlen M, Wolff E. Investigations concerning the constants "β" and "r" according to Widmark especially in women. Acta Pathol Microbiol Scand Suppl 1944;54:489-498.

12. Jokipii SG. Experimental studies on blood alcohol in healthy subjects and in some diseases. Ann Med Exp Biol Fenn 1951;29(2):1–99.

13. Lentner C, editor. Geigy Scientific Tables Volume 3: Physical Chemistry, Composition of Blood, Hematology, Somatometric Data. 8th ed. Ciba-Geigy, 1984. p359

14. Maskell PD, Jones AW, Savage A, Scott-Ham M. Evidence based survey of the distribution volume of ethanol: Comparison of empirically determined values with anthropometric measures. Forensic Sci Int 2019;294:124–31. https://doi.org/10.1016/j.forsciint.2018.10.033.

15. Gullberg RG, Jones AW. Guidelines for estimating the amount of alcohol consumed from a single measurement of blood alcohol concentration: re-evaluation of Widmark's equation. Forensic Sci Int 1994;69(2):119–30. https://doi.org/10.1016/0379-0738(94)90248-8.

16. Maskell PD, Alex Speers R, Maskell DL. Improving uncertainty in Widmark equation calculations: Alcohol volume, strength and density. Sci Justice 2017;57(5):321–30. https://doi.org/10.1016/j.scijus.2017.05.006.

17. Maskell PD, Holmes C, Huismann M, Reid S, Carr M, Jones BJ, et al. The influence of alcohol content variation in UK packaged beers on the uncertainty of calculations using the Widmark equation. Sci Justice 2018;58(4):271–5. https://doi.org/10.1016/j.scijus.2018.03.003.

18. Reid S, Maskell PD, Maskell DL. Uncertainty in Widmark calculations: ABV variation in packaged versions of the most popular beers in the UK. Sci Justice 2019;59(2):210–3. https://doi.org/10.1016/j.scijus.2018.11.005.

19. Gullberg RG. Estimating the measurement uncertainty in forensic blood alcohol analysis. J Anal Toxicol 2012;36(3):153–61. https://doi.org/10.1093/jat/bks012.

20. Jones AW, Andersson L. Influence of age, gender, and blood-alcohol concentration on the disappearance rate of alcohol from blood in drinking drivers. J Forensic Sci 1996;41(6):922–6.

21. Jones AW. Alcohol, its absorption, distribution, metabolism, and excretion in the body and pharmacokinetic calculations. Wiley Interdiscip Rev Forensic Sci 2019;1(5). https://doi.org/10.1002/wfs2.1340.

Table 1: Mean (± SD) of alcohol elimination rate (β), ethanol volume of distribution (r) and total body water (TBW) in a series of studies where individuals were administered a bolus of alcohol on an empty stomach following and overnight fast.

Study	Males				Females				Males & Females Combined			
	n	β (mg/100mL/h)	r (L/kg)	TBW (L)	n	β (mg/100mL/h)	r (L/kg)	TBW (L)	n	β (mg/100mL/h)	r (L/kg)	TBW (L)
Springer (9)	22	12.67 ± 2.23	0.77 ± 0.07	46.55 ± 5.42	10	14.93 ± 2.28	0.67 ± 0.06	31.66 ± 4.71	32	13.42 ± 2.46	0.74 ± 0.08	41.59 ±8.77
Mallach (10)	25	17.31 ± 3.48	0.69 ± 0.12	42.94 ± 7.63								
Freudenberg and Mallach (8)									55	**15.68 ± 3.42**	**0.71 ± 0.09**	**41.38 ± 7.39**
Osterlind (11)	10	12.41 ± 2.07	0.70 ± 0.07	42.64 ± 6.71	20	14.78 ± 2.04	0.64 ± 0.07	31.94 ± 3.78	30	13.99 ± 2.31	0.66 ± 0.08	35.51 ± 7.04
Jokipii (12)	19	12.59 ± 2.03	0.72 ± 0.10	39.69 ± 7.59	23	13.95 ± 2.09	0.66 ± 0.08	32.53 ± 7.01	42	13.34 ± 2.15	0.69 ± 0.10	35.77 ± 8.04
ALL	76	14.14 ± 3.43	0.72 ± 0.10	43.13 ± 7.25	53	14.46 ± 2.12	0.65 ± 0.08	32.14 ± 5.46	184*	**14.69 ± 3.16**	**0.70 ± 0.10**	**39.40 ± 8.27**

*The 184 individuals includes all the data from references (8–12).

Table 2: Variance of all of the terms for variability equations

	%CV	Reference
e_v = coefficient of variance of the volume of drink consumed	See table 5 of reference for details. **Commonly - 2.35%**	(16)
e_z = coefficient of variance of the alcoholic strength of the drink consumed	Depends on ABV needs to be calculated from SD **"Craft" Beer (SD) - ± 0.48%v/v** **"Commercial" Beer (SD)- ± 0.1%v/v**	(17) (18)
e_d = coefficient of variance of density of alcohol (ethanol)	Considered a constant	(16)
e_B = coefficient of variance of the blood alcohol analysis result	Determined from the Measurement variability of the analytical method being used commonly 5%.	(19)
e_β = coefficient of variance of alcohol elimination rate	**26.3**	(20)
e_t = coefficient of variance of the duration of the drinking session	Based on case information	n/a
eTBW = coefficient of variance of the total body water of the subject	**9.09**	(5)
eF_{water} = coefficient of variance of fraction of blood volume that is water	Considered a constant	(5,21)