Predictive Performance of the Winter-Tozer and Its Derivative Equations for Estimating Free Phenytoin Concentrations in Specific Patient Populations

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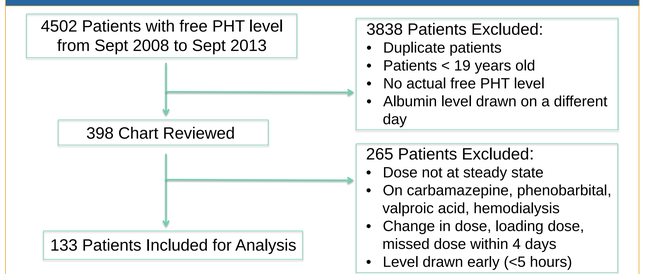
Background

- Free phenytoin (PHT) concentration reflects efficacy and toxicity
- Low albumin concentration may affect total PHT concentration and free fraction, but usually causes no change in free concentration
  - Cannot estimate free PHT concentration from total PHT concentration when free fraction is unknown
- Winter-Tozer equation most commonly used to predict free PHT concentration
- Overall predictive performance of this equation is poor
- Other studies found bias and imprecision and developed their own equations, which have not been validated in other studies

Methods

- Retrospective chart review at Vancouver General Hospital from Sept 2008 to Sept 2013
- Inclusion: > 18 years old, free PHT level
- Exclusion: level is not at steady state; patients on carbamazepine, phenobarbital, valproic acid, and hemodialysis
- Convenience sample size of ~50 patients per subgroup (Critical Care, General Medicine, Neurology)
- Mean predictive error (MPE) to assess bias and root mean square error (RMSE) to assess precision
- Primary objective:
  - To assess the bias and precision of the Winter-Tozer equation and its derivatives in predicting free PHT concentrations in different patient subpopulations
- Secondary objective:
  - To assess the effect of age, gender, eGFR, and total daily dose on the bias and precision of the Winter-Tozer equation and its derivatives
  - To derive new equations that will better predict free PHT concentration

Exclusion Flow Chart



Predictive Equations

Equation 1 (Winter-Tozer)[1]

$$\text{Predicted Free PHT} = \frac{\text{Measured Total PHT}}{(0.2\times\text{Albumin} + 0.1)} \times 0.1$$

Equation 2 (Kane et al.)[2]

$$\text{Predicted Free PHT} = \frac{\text{Measured Total PHT}}{(0.29\times\text{Albumin} + 0.1)} \times 0.1$$

Equation 3 (Kane et al.)[2]

$$x = -0.40378 + (\text{Measured Total PHT}\times 0.17807) + (\text{Measured Total PHT}^2\times -0.00328) + (\text{Albumin}\times -0.31312) + (\text{Male}\times 0.12362) + (\text{CrCl}\times -0.00174)$$
$$\text{Predicted Free PHT} = e^x$$

Equation 4 (Anderson et al.)[3]

$$\text{Predicted Free PHT} = \frac{\text{Measured Total PHT}}{(0.25\times\text{Albumin} + 0.1)} \times 0.1$$

$$\text{MPE}^4 = \frac{1}{n}\Sigma(\text{P.E.})$$

$$\text{RMSE}^4 = \sqrt{\left[\frac{1}{n}\Sigma(\text{P.E.})^2\right]}$$

Phenytoin (PHT) in µg/mL (x 4 to get µmol/L)
Albumin in g/dL (x 10 to get g/L)
PE = Predictive Error

[1] Applied Therapeutics. 1992:25.1–25.44.
[2] Ann Pharmacother. 2013;47:628–36.
[3] Ann Pharmacother. 1997;31:279–84.
[4] Clin Pharm. 1987;6:888–94.

Table 1: Summary of Baseline Characteristics

Characteristic (SD)	All (n = 133)	Critical Care (n = 36)	General Medicine (n = 56)	Neurology (n = 41)
Age	63.9 (18.9)	57.0 (17.9)	74.0 (14.0)	56.0 (20.0)
Gender, Male (n, %)	71 (53%)	26 (72%)	24 (43%)	21 (51%)
SrCr (µmol/L)	90.4 (64.0)	104 (74.8)	96.8 (75.0)	70.3 (16.3)

Table 2: Bias and Precision Per Subgroup

Equation	All (n = 133)	Critical Care (n = 36)	General Medicine (n = 56)	Neurology (n = 41)
Bias (MPE) (95% CI) (µmol/L)				
1	**1.7** (1.5 to 1.9)	**1.4** (0.7 to 2.1)	**1.7** (1.4 to 2.0)	**1.9** (1.6 to 2.2)
2	**-0.2** (-0.4 to 0.0)	**-0.9** (-1.6 to -0.2)	**-0.1** (-0.3 to 0.1)	**0.2** (0.0 to 0.4)
3	**-0.3** (-0.5 to -0.1)	**-1.1** (-1.7 to -0.5)	**5.0** (4.7 to 5.3)	**0.2** (0.0 to 0.4)
4	**0.5** (0.3 to 0.7)	**0.0** (-0.7 to 0.7)	**0.5** (0.3 to 0.7)	**0.9** (0.7 to 1.1)
Precision (RMSE) (95% CI)				
1	**2.2** (1.2 to 3.2)	**2.5** (0.3 to 4.8)	**2.1** (0.4 to 3.8)	**2.2** (0.9 to 3.5)
2	**1.4** (0.2 to 2.6)	**2.3** (-1.8 to 6.4)	**0.9** (0.3 to 1.3)	**0.7** (0.5 to 0.9)
3	**1.3** (0.5 to 2.1)	**2.0** (-0.4 to 4.4)	**1.1** (0.4 to 1.8)	**0.8** (0.6 to 1.0)
4	**1.4** (0.6 to 2.2)	**2.0** (-0.8 to 4.8)	**1.1** (0.6 to 1.6)	**1.1** (0.7 to 1.5)

Figure 1: Bland-Altman Plots for All Patients, Critical Care, General Medicine, and Neurology

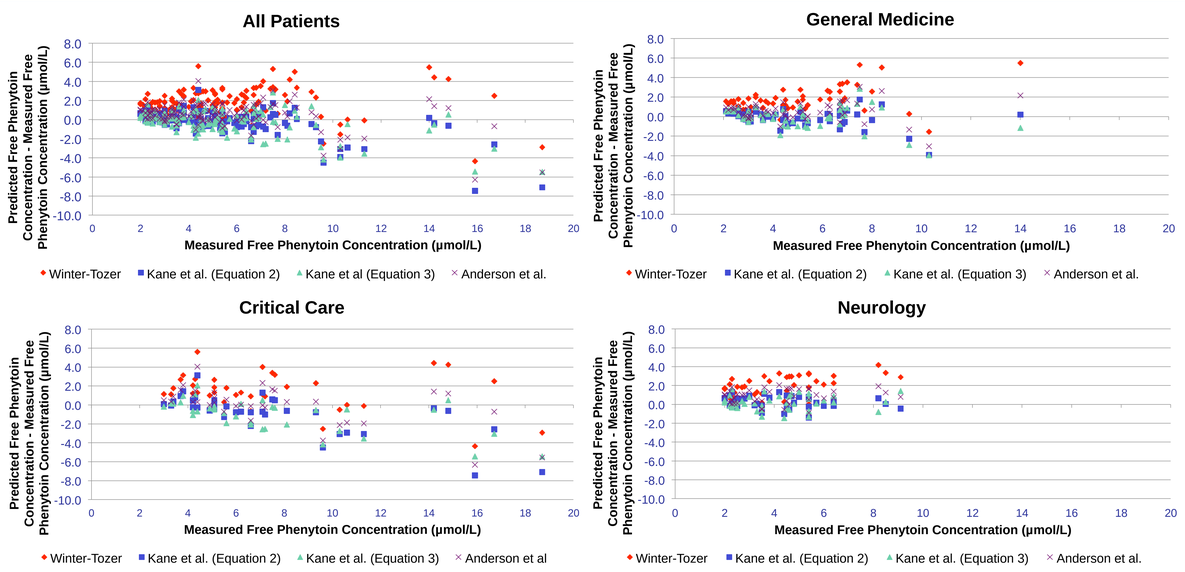


Table 3: Bias and Precision for Age, Gender, and eGFR

MPE (µmol/L) /RMSE (95% CI)	Equation 1	Equation 2	Equation 3	Equation 4	MPE (µmol/L) /RMSE (95% CI)	Equation 1	Equation 2	Equation 3	Equation 4
≤ 60 years (n = 53)	**1.6** (1.2 to 2.0)	**-0.3** (-0.8 to 0.2)	**-0.5** (-0.9 to -0.1)	**0.4** (0.0 to 0.8)	**eGFR <30** (mL/min) (n = 6)	**-0.1** (-2.4 to 2.2)	**-2.5** (-5.0 to 0.0)	**-1.3** (-3.5 to 0.9)	**-1.6** (-4.0 to 0.8)
	2.2 (1.1 to 3.3)	**1.7** (-1.1 to 4.5)	**1.5** (-0.1 to 3.1)	**1.6** (-0.3 to 3.5)		**2.6** (-3.0 to 8.2)	**3.8** (-13.5 to 21.1)	**2.9** (-7.0 to 12.8)	**3.2** (-9.2 to 15.6)
> 60 years (n = 80)	**1.8** (1.5 to 2.1)	**-0.2** (-0.4 to 0.0)	**-0.1** (-0.4 to 0.2)	**0.5** (0.3 to 0.7)	**30-59** (n= 27)	**1.3** (0.8 to 1.8)	**-0.5** (-0.9 to -0.1)	**-0.3** (-0.8 to 0.2)	**0.2** (-0.2 to 0.6)
	2.8 (1.3 to 4.3)	**1.4** (0.8 to 2.0)	**1.5** (0.9 to 2.1)	**1.5** (0.9 to 2.1)		**1.9** (-0.4 to 4.2)	**1.2** (-0.1 to 2.5)	**1.3** (-0.1 to 2.7)	**1.1** (0.2 to 2.0)
Male (n = 71)	**1.7** (1.3 to 2.1)	**-0.2** (-0.6 to 0.2)	**-0.1** (-0.4 to 0.2)	**0.5** (0.2 to 0.8)	**60-89** (n = 54)	**2.0** (1.7 to 2.3)	**-0.1** (-0.5 to 0.3)	**0.0** (-0.4 to 0.4)	**0.7** (0.4 to 1.0)
	2.3 (0.8 to 3.8)	**2.3** (0.8 to 3.8)	**1.3** (0.2 to 2.4)	**1.5** (0.1 to 2.9)		**2.4** (1.1 to 3.7)	**1.3** (-0.5 to 3.1)	**1.3** (0.1 to 2.5)	**1.4** (0.3 to 2.5)
Female (n = 62)	**1.7** (1.4 to 2.0)	**-0.2** (-0.5 to 0.1)	**-0.4** (-0.7 to -0.1)	**0.5** (0.2 to 0.8)	**≥ 90** (n = 46)	**3.1** (2.7 to 3.5)	**0.1** (-0.1 to 0.3)	**-0.6** (-0.9 to -0.3)	**1.2** (0.9 to 1.5)
	2.2 (0.8 to 3.6)	**1.1** (0.2 to 2.0)	**1.4** (0.5 to 2.3)	**1.2** (0.6 to 1.8)		**2.9** (1.0 to 4.8)	**1.0** (0.6 to 1.4)	**1.3** (0.9 to 1.7)	**1.5** (0.8 to 2.2)

Table 3 (continued): Bias and Precision for Total Daily Dose

Dose (mg)	Analysis (95% CI)	Equation 1	Equation 2	Equation 3	Equation 4
< 300 (n = 18)	MPE (µmol/L)	**1.7** (1.1 to 2.3)	**-0.2** (-0.5 to 0.1)	**-0.3** (-0.8 to 0.2)	**0.5** (0.1 to 0.9)
	RMSE	**2.1** (-1.2 to 5.4)	**0.7** (0.4 to 1.0)	**1.2** (0.4 to 2.0)	**1.0** (0.5 to 1.5)
300 (n = 53)	MPE (µmol/L)	**1.5** (1.0 to 2.0)	**-0.6** (-1.1 to -0.1)	**-0.6** (-1.0 to -0.2)	**0.2** (-0.3 to 0.7)
	RMSE	**2.3** (0.6 to 4.0)	**1.8** (-1.0 to 4.6)	**1.6** (-0.1 to 3.3)	**1.7** (-0.1 to 3.5)
301-499 (n = 43)	MPE (µmol/L)	**1.7** (1.3 to 2.1)	**-0.1** (-0.4 to 0.2)	**-0.1** (-0.4 to 0.2)	**0.6** (0.3 to 0.9)
	RMSE	**2.0** (0.7 to 3.3)	**0.9** (0.0 to 1.8)	**0.9** (0.1 to 1.7)	**1.1** (0.4 to 1.8)
≥ 500 (n = 19)	MPE (µmol/L)	**2.3** (1.7 to 2.9)	**0.2** (-0.4 to 0.8)	**0.3** (-0.3 to 0.9)	**1.0** (0.5 to 1.5)
	RMSE	**2.6** (-0.6 to 5.8)	**1.2** (-0.1 to 2.5)	**1.3** (0.0 to 2.6)	**1.5** (-0.2 to 3.2)

Table 4: Bias and Precision of New Equations

$$\text{Predicted Free PHT} = \frac{\text{Measured Total PHT}}{(\text{'?'}\times\text{Albumin} + 0.1)} \times 0.1$$

Analysis (95% CI)	Equation X '0.26'	Equation Y '0.27'	Equation Z '0.28'	Equation W '0.275'
MPE (µmol/L)	**0.3** (0.1 to 0.5)	**0.1** (-0.1 to 0.3)	**-0.1** (-0.3 to 0.1)	**0.0** (-0.2 to 0.2)
RMSE	**1.3** (0.4 to 2.2)	**1.3** (0.3 to 2.3)	**1.3** (0.3 to 2.3)	**1.3** (0.2 to 2.4)

Figure 2: Bland-Altman Plot of New Equations

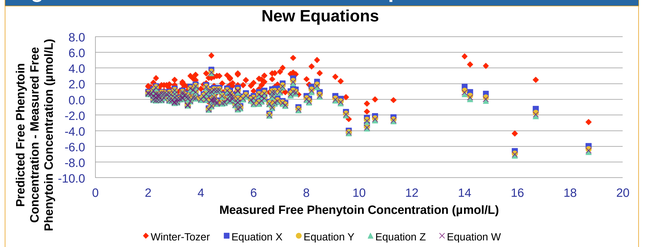


Table 5: Dose Changes Made From Predictive Equations

Equation	Actual	1	2	3	4	X	Y	Z	W
> 8 µmol/L	18	43	16	15	26	23	20	16	19
Changes to Dose (n)		25	2	3	8	5	2	2	1
< 4 µmol/L	47	21	48	49	36	38	39	44	43
Changes to Dose (n)		26	1	2	11	9	8	3	4
Total (n, %)		**51 (38)**	**3 (2)**	**5 (4)**	**19 (14)**	**14 (11)**	**10 (8)**	**5 (4)**	**5 (4)**

Results

- The Winter-Tozer equation tended to overpredict
- The Kane et al. equations (Equation 2 and 3) tended to underpredict
- The Anderson et al. equation generally overpredicted
- In general, there was more bias and imprecision associated with the Winter-Tozer equation than the other equations

Conclusion

- The overall predictive performance of the Winter-Tozer equation in this population was poor
- We developed new derivative equations with reduced bias

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