Predictive Performance of the Winter-Tozer and Its Derivative Equations for Estimating Free Phenytoin Concentrations in Neurology Patients on Concurrent Enzyme Inducers (Phenobarbital, Carbamazepine) and Inhibitors (Valproic Acid) Catharina Yih, B.Sc.(Pharm.); Tony Kiang, B.Sc.(Pharm.), Ph.D., ACPR; Greg Egan, B.Sc.(Pharm.), ACPR; Greg Egan, B.Sc.(Pharm.), Ph.D.;

Mary H. H. Ensom, B.S.(Pharm.), Pharm.D., FASHP, FCCP, FCSHP, FCAHS

Backgro	und		Predictive Equations			Table 2: Bias and Precision by Interaction						
•Phenytoin (I	PHT) highly bound	to albumin			Equation 1	Predicted Free	РНТ	Equa-	All (n=44)	VPA (n=15)	CBZ (n=22)	PB (n=9)
•Efficacy & to	oxicity determined k	oy free conce	ntration		(Winter-Tozer) ¹	= Measured Tota (0.2 x Albumin	al PHT + 0.1) x 0.1	Bias (MP	E) (95%CI) (j	umol/L)	(
•Protein bind	ding affected by dru	g interactions	5			× ·		1	1.3 (0.8 to 1.	8) 0.2 (-0.6 to 1.0)	2.1 (1.5 to 2.7)	0.8 (-0.6 to 2.2)
•Most comm	nonly used equation				Equation 2*	Predicted Free Pl	HT	2	- 1.8 (-2.5 to -7	-2.1 (-3.5 to -0.7)	-0.7 (-1.8 to 0.4)	-2.9 (-4.8 to -1.0) (n =5)
•Winter-Ic	ozer: poor predictive	e performanc	e, developed	in absence	(May et al.) ²	=[0.0792 + (0.0 x Measured To	000636 x VPA)] otal PHT	3	-0.6 (-1.3 to 0	-0.6 (-1.9 to 0.7)	0.2 (-1.0 to 1.4)	-0.7 (-3.3 to 1.9)
	ting arugs	studied in lite	oratura		Equation 3*	Predicted Free PH	HT	4	(<i>n</i> =30) - 0.9 (-1.4 to -(-1.8 (-2.9 to -0.7)	(n=10) 0.0 (-0.4 to 0.4)	(<i>n</i> =5) - 1.8 (-3.1 to -0.5)
	ations developed 12	acked hypoall	huminemic na	atients	(Haidukewych	=[0.095 + (0.00	01 x VPA)]	5	-1.2 (-1.9 to -0	-1.9 (-3.0 to -0.8)	-0.1 (-0.5 to 0.3)	-2.7 (-5.2 to -0.2)
•VPA disp	places PHT from alb	oumin, inhibits	et al.) ³	x Measured To	ital PH I	6	-0.6 (-1.1 to -0	0.1) -1.6 (-2.6 to -0.6)	0.3 (-0.1 to 0.7)	-1.5 (-2.8 to -0.2)		
•Carbamaze	pine (CBZ) likely in	duces CYP20	C19		Equation 1	Prodicted Free F	оцт	Precision	(RMSE) (95	%CI)		
•Phenobarbi	ital (PB) induces CY	(P2C9 and C)	YP3A4 enzyr	nes	(Kane et al.) ⁴	= Measured Tota	$\frac{1}{1}$ PHT x 0.1	1	2.2 (0.0 to 4.	4) 1.5 (-0.6 to 3.6) 3.4 (44.0 to 40.7)	2.5 (-1.3 to 6.3)	2.2 (-2.1 to 6.5)
 No equation 	ns developed to acc	count for CBZ	, PB interacti	ons		(0.29 x Albumin	n + 0.1)	2	(n=30)	J.2) J.4 (-11.9 (0 18.7)	(n=10)	(n =5)
Methods					Equation 5	x = -0.40378		3		.5) 2.6 (-7.4 to 12.6)	1.8 (-1.6 to 5.2) (<i>n</i> =10)	3.6 (-10.0 to 17.2) (<i>n</i> =5)
•Retrospectiv	ve chart review at \	/ancouver Ge	eneral Hospita	al from Aug	(Kane et al.) ⁴	+ (Measured Total PHT + (-0.00328 x Measure	PHT x 0.17807) sured Total PHT ²)	4	2.1 (-1.2 to 5	.4) 2.7 (-5.8 to 11.2)	0.9 (0.3 to 1.5)	2.6 (-5.4 to 10.6)
2005 - Aug 2014						+ (-0.31312 x Albui	min)	5	2. <i>(</i> -3.5 to 8 1.9 (-1.0 to 4)	$\begin{array}{c} \textbf{.9} \\ \textbf{2.9} (-6.6 \text{ to } 12.4) \\ \textbf{2.5} (-5.0 \text{ to } 10.0) \\ \end{array}$	0.9 (0.5 to 1.3) 1 0 (0.3 to 1.7)	4.5 (-20.9 to 29.9)
•Convenienc	ce sample ~30 patie	ents per intera	acting medica	tion		+ (0.12362 X Male)) + (-0.00174 X CICI)	Tabla	2. Dies e			
(VPA, PB, C	BZ)	-				Predicted Free PH	Predicted Free PHT = e ^x		J. DIAS a			tion Equation
• <u>Inclusion:</u> ≥	18 years old, stead	dy state PHT	free & total co	oncentrations	Equation 6	Predicted Free	PHT	(µmol/L)/	Equation	2 3	A Equation Equation Equation 4	ation Equation 6
• <u>Exclusion:</u> F	Hemodialysis, pregr	nancy			(Cheng et al.) ⁵	= Measured To	$\frac{\text{otal PHT}}{\text{min} + 0.1} \times 0.1$	RMSE (95% CI)				
•Mean predic	ction error (MPE) to	b assess blas	and root mea	an square		(0.275 X Album	nin + 0.1)	≤ 60	1.6	-1.2 0.3	-0.7 -	1.1 -0.4
Primary obj	c) to assess precision	n			MPE= $\frac{1}{n}\sum PE$	* CBZ, PB substitute	d for VPA in	years (n= 24)	(0.8 (0 2.4)	(-1.9 10 - 0.5) $(-0.5 10 - 1.)(n=18)$ $(n=18)$	1) (-1.3 (0 -0.1) (-2.1	(-1.0 (0 0.2)
•To asses	<u>ective.</u> is the accuracy and	nrecision of t	the Winter-To	zer equation		applicable subgroups	S		2.5	1.9 1.7	1.7 2	.8 1.6
and other	identified equation:	s in estimatin	a free phenvt	oin	RMSE= $\left \frac{1}{\pi}\sum (PE)^2\right $		¹ Applied Therapeutics. 1992;25.1-25.44. ² Eur Neurol. 1991;31: 57-60. ³ Ther Drug Magit		(-1.1 to 6.1)	(-1.1 to 4.9) (0.6 to 2.8 (n=18) (n=18)	3) (-0.7 to 4.1) (-7.0	o 12.6) (-0.5 to 3.7)
concentra	ations in neurology p	patients taking	g concurrent	enzyme	√n∠			> 60	0.8	-2.7 -1.4	- 1.2 -	1.4 -0.9
inducers/i	inhibitors				Phenytoin (PHT) in µg/mL (4 to get µmol/L)	⁴ 1989;11:134-9.	years (n= 20)	(0.0 to 1.6)	(-4.6 to -0.8) $(-3.3 to 0.8)(n=12)$ $(n=12)$	b) (-2.2 to -0.2) (-2.4	(-1.8 to 0.0)
Frelusio	n Flow Chart				VPA in μ g/mL (x 6.94 to get CBZ in μ g/mL (x 4.23 to get	µmol/L)	2013;47:628-36. ⁵ Pharmacotherapy		1.9	4.3 3.5	2.4 2	.7 2.3
		7			PB in μ g/mL (x 4.23 to get μ	mol/L)	(Abstract). 2014;34: #144 (p. e214) DOI:		(-0.2 to 4.0)	(-16.3 to 24.9) (-10.8 to 17 (n=12) (n=12)	.8) (-4.5 to 9.3) (-4.9	o 10.3) (-3.8 to 8.4)
1112 patient	t account numbers	967 patient	account numb	ers excluded:	PE = predictive error		10.1002/phar.1497					
with PHT a	nd/or interacting	•Duplicate p	atients (n=21)		Figure 1: Bland-A	Itman Plots for	rbamazepine, Phenobarbital, and Valproic Acid					
Aug 2014	5 IIOIII Aug 2005 –	•No free PH	T level (n=650)	a(n-20)		All Patients	nts			Carban	nazepine	
		•No VPA leve	el for patients in	VPA group		•			Free mol/L		•	
		(n=91)					Equation	1	enytol ured on (µr			 Equation 1
		•Albumin lev PHT level (n	nin level not drawn within 24 hours of evel (n=151)			• Equation	2	e Phe Meas ntratio	• •		Equation 2	
	,	 Patient not at VGH (n=14) Hemodialysis patient (n=1) 8 89 patients excluded: 				Equation 3 × Equation 4 × Equation 5	3				× Equation 4	
145 patient	account numbers				■ ** ★		5	edicte entrat toin C			× Equation 5	
(132 differen	nt patient charts					Equation	6	Processon Proces			 Equation 6 	
reviewed)												
	•PHT le •Level o		evel drawn early (<6h after dose) (n=3)		0 2 4 Measured	6 8 10 12 14 16 18 20 Free Phenytoin Concentration (μmol/L)			0 N	0 2 4 6 8 Measured Free Phenytoin Concentration (µm		0 12 DI/L)
		 Did not receive both drugs together (n=10) Chart not accessible (confidential 				Valproic Acid	Valproic Acid			Phenobarbital		
44 PHT leve	els included for	n=2, offsite r	n=1)			•						
analysis (45	s patients)				0.0 (h		 Equation 1 		sured on (µr	•		 Equation 1
Table 1: Su	ummary of Base	eline Chara	cteristics				Equation 2		ee Ph Meas entrati			Equation 2
Characteristic	Mean All	Valproic Acid	Carbamazepine	Phenobarbital	Conce Fr		× Equation 4		ed Fre		× ^ • *	— × Equation 4
	(N=44) 57.2 (27.0)	(n=15)	(n=22)	(n=9) 68 7 (17 0)	v° ∕toin (Ж	₹ Equation 5		edicte toin C	▲	•	— × Equation 5
Male (n %)	27(61%)	8 (53%)	14 (61%)	7 (78%)			Equation 6		-10.0 Conc			 Equation 6
SCr (umol/L)	64.8 (21.4)	52.9 (16.4)	69.2 (21.4)	75.1 (19.7)	-12.0	6 9 10 12	16 10 20		-12.0	2 4 5 5	10 12 14	10
Albumin \leq 34 g/L ((n,%) 31 (70%)	14 (93%)	15 (68%)	4 (44%)	0 2 4 Measured	Free Phenytoin Concentrati	ion (µmol/L)		0	Measured Free Phenytoi	n Concentration (µmol/L	.)
			· /		1							
f	racorhoal	h Van	couver /		Travidonce		Provincial	Healt	1 I			
		ll Coa	stalHe	alth 🐸	HEALTH CAR	T	Convinces A	uthori	τγ			
Be	etter health. Best in health	care. Prom	noting wellness. Ens	uring care.	How you want to h	e treated	Better health		0.			
					TIOW YOU WAILLOD	c incateu.						

Background		Predictive Equations				Table 2: Bias and Precision by Interaction					
 Phenytoin (PHT) highly bound to 	o albumin	Equation 1	Predicted Free PH	ΗT	Equa-	AII	VPA	CBZ	PB (n=9)		
 Efficacy & toxicity determined b 	y free concentration	(Winter-Tozer) ¹	$= \frac{\text{Measured Total F}}{(0.2 \times \text{Albumin I})}$	$\frac{PHT}{0.1} \times 0.1$	tion Bias (MPI	(n=44) =) (95%Cl) (um	(n=15)	(n=22)	(n=9)		
 Protein binding affected by drug 	g interactions		(U.2 X Albumin +)	0.1)	1	1.3 (0.8 to 1.8)	0.2 (-0.6 to	1.0) 2.1 (1.5 to 2.7) 0.8 (-0.6 to 2.2)		
 Most commonly used equation: 		Equation 2*	Predicted Free PH	т	2	-1.8 (-2.5 to -1.1)	-2.1 (-3.5 to	-0.7) -0.7 (-1.8 to 0.4	4) -2.9 (-4.8 to -1.0)		
 Winter-Tozer: poor predictive 	e performance, developed in absence	(May et al.) ²	=[0.0792 + (0.00	00636 x VPA)]	3	(<i>n</i> =30)	-0 6 (_1 9 to	(n=10)	($n = 5$)		
of interacting drugs		Equation 2*	x Measured Tota	al PHT -	5	(n=30)	-0.0 (-1.9 ແ	(n=10)	(n =5)		
 Valproic acid (VPA) interaction 	studied in literature	(Haidukewych	=[0.095 + (0.001	x VPA)]	4	-0.9 (-1.4 to -0.4)	-1.8 (-2.9 to	0.0 (-0.4 to 0.4	 -1.8 (-3.1 to -0.5) 2.7 (-5.0 to -0.5) 		
 Two equations developed, la 	cked hypoalbuminemic patients	et al.) ³	x Measured Tota	I PHT	5	- 1.2 (-1.9 to -0.5)	-1.9 (-3.0 to	-0.8) -0.1 (-0.5 to 0.3)	-2.7 (-5.2 to -0.2)		
•VPA displaces PH1 from alb	umin, inhibits PHT metabolism				Precision	(RMSE) (95%C	- 1.0 (-2.0 ic) -1.3 (-2.8 (0 -0.2)		
•Carbamazepine (CBZ) likely ind	JUCES CYP2C19	Equation 4	Predicted Free PH	IT.	1	2.2 (0.0 to 4.4)	1.5 (-0.6 to	2.5 (-1.3 to 6.3	3) 2.2 (-2.1 to 6.5)		
•Phenobarbilar (PB) induces C r	PZC9 and CTP3A4 enzymes	(Kane et al.) ⁴	= 1000000000000000000000000000000000000	0.1) x 0.1	2	3.2 (-3.8 to 10.2)	3.4 (-11.9 to	18.7) 1.8 (-2.9 to 6.5	5) 3.9 (-13.7 to 21.5)		
					3	(<i>n=30</i>) 2.6 (-2.3 to 7.5)	2.6 (-7.4 to	(<i>n</i> =10) 12.6) 1.8 (-1.6 to 5.2	(<i>n</i> =5) 2) 3.6 (-10.0 to 17.2)		
Methods		Equation 5	x = -0.40378		4	(n=30)		(n=10)	(n =5)		
 Retrospective chart review at V 	ancouver General Hospital from Aug	(Kane et al.) ⁴	+ (-0.00328 x Measu	red Total PHT ²)	4	2.1 (-1.2 to 5.4)	2.1 (-5.8 to	11.2) U.9 (0.3 to 1.5) 2.b (-5.4 to 10.6)) 4.5 (-20.9 to 29.9)		
2005 – Aug 2014			+ (-0.31312 x Albumin) + (0.12362 x Male) + (-0.00174 x CrCl)		6	1.9 (-1.0 to 4.8)	2.5 (-5.0 to	10.0) 1.0 (0.3 to 1.7) 2.3 (-20.9 to 29.9)) 2.3 (-5.2 to 9.8)		
 Convenience sample ~30 patie 	nts per interacting medication				Tabla	2. Riac and	d Procisio		, , , ,		
(VPA, PB, CBZ)			Predicted Free PHT = e ^x			5. DIAS AIN			Equation Equation		
 Inclusion: ≥ 18 years old, stead 	y state PHT free & total concentrations	Equation 6	Predicted Free Pl	НТ	(µmol/L)/	Equation Eq	ation Equ	4	Equation Equation 5 6		
 Exclusion: Hemodialysis, pregn 	ancy	(Cheng et al.) ⁵	= Measured Total	<u>I PHT</u> x 0.1	RMSE (95% CI)						
 Mean prediction error (MPE) to 	assess bias and root mean square		(0.275 x Albumin + 0.1)		≤ 60	1.6	-1.2	0.3 -0.7	-1.1 -0.4		
error (RMSE) to assess precisio	n	MPE= $\frac{1}{2}\sum PE$	* CBZ, PB substituted for VPA in		years (n= 24)	(0.8 to 2.4) (-1	.9 to -0.5) (-0. (<i>n</i> =18) (5 to 1.1) (-1.3 to -0.1) n=18)	(-2.1 to -0.1) (-1.0 to 0.2)		
• <u>Primary objective:</u>		n 🚄	applicable subgroups		()	2.5	1 0	17 17	29 16		
 To assess the accuracy and and other identified equations 	precision of the winter-lozer equation	$PMSE = \frac{1}{2} \sum (PE)^2$		¹ Applied Therapeutics. 1992:25.1-25.44.		(-1.1 to 6.1) (-1	1.1 to 4.9) (0.0	6 to 2.8) (-0.7 to 4.1)	(-7.0 to 12.6) (-0.5 to 3.7)		
concontrations in nourology n	ationts taking concurrent onzymo		4 to get µmol/L)	² Eur Neurol. 1991;31: 57-60.	> 60	0.8	(<i>n</i> =18) (-2.7	-1.4 -1.2	-1.4 -0.9		
inducers/inhibitors	allents taking concurrent enzyme	Phenytoin (PHT) in µg/mL (x		³ Ther Drug Monit. 1989:11:134-9.	years	(0.0 to 1.6) (-4	(-3.) (n=12)	3 to 0.5) (-2.2 to -0.2) n=12)	(-2.4 to -0.4) (-1.8 to 0.0)		
		Albumin in g/dL (x 10 to get g VPA in ug/mL (x 6.94 to get u	g/L) umol/L)	⁴ Ann Pharmacother. 2013;47:628-36.	(n= 20)			,			
Exclusion Flow Chart		CBZ in μ g/mL (x 4.23 to get μ PB in μ g/mL (x 4.31 to get μ r	µmol/L)	⁵ Pharmacotherapy. (Abstract). 2014;34:		1.9 (-0.2 to 4.0) (-16	4.3 6.3 to 24.9) (-10.	3.52.4 8 to 17.8)(-4.5 to 9.3)	2.7 2.3 (-4.9 to 10.3) (-3.8 to 8.4)		
1112 patient account numbers		PE = predictive error		, #144 (p. e214) DOI: 10.1002/phar.1497			(n=12) (n=12)			
with PHT and/or interacting	967 patient account numbers excluded:	Figure 1: Bland-Altman Plots for All Patients, Carbamazonine, Phonobarbital, and Valoroic A									
drug orders from Aug 2005 –	•No free PHT level (n=650)	Figure 1. Dianu-Altman Flots for All Patients, Car				bamazepine, r nenobarbital, and valproit Aciu					
Aug 2014	•PHT level not at steady state (n=39)		All Patients			0.8 []	Ca	rbamazepine			
	•No VPA level for patients in VPA group		•			Vtoin ed Fre		•	Equation 1		
	•Albumin level not drawn within 24 hours of			Equation Equation	1 2	ation		•	Equation 1		
	PHT level (n=151)	0.0 Mea		Equation	3		· · · · · ·	× ×	Equation 3		
↓ 115 nationt account numbers	 Patient not at VGH (n=14) Homodialysis patient (n=1) 			×Equation	4	Conce Field			Equation 4		
(132 different patient charts	Themoularysis patient (II-T)		■ <u> </u>	Equation 5	5		•	**** ***	× Equation 5		
reviewed)	90 notionto ovoludodu		 Equation 6 8 10 12 14 16 18 20 Free Phenytoin Concentration (μmol/L) 		0		A				
	•PHT level not at steady state (n=73)	$-12.0 \qquad \blacksquare \qquad \times \qquad 0 \qquad 2 \qquad 4$				-6.0	•				
	→ •Level drawn early (<6h after dose) (n=3)	Measured F				Meas	0 2 4 6 8 10 Measured Free Phenytoin Concentration (µmol/		ol/L)		
	 Did not receive both drugs together (n=10) Chart not accessible (confidential) 		Valoroja A aid	Valoroic Acid							
44 PHT levels included for	n=2, offsite n=1)						Р	nenoparbitai			
analysis (43 patients)				Equation	1	vytoin ed Fr 90	•	A	 Equation 1 		
Table 1: Summary of Base	line Characteristics	0.0 Dher ration		Equation :	2				Equation 2		
Characteristic Mean All	Valoroic Acid Carbamazenine Phenobarbital			Equation :	3				Equation 3		
(SD) (n=44)	(n=15) (n=22) (n=9)	n Cor 0.9-		× Equation	5			◆ ×	Equation 4		
Age (years) 57.2 (27.0)	56.6 (19.8) 52.3 (20.3) 68.7 (17.0)	Pred 0.8-		Equation	5	Predi nytoir -80	<u>۸</u>	*	Equation 5 Equation 6		
Male (n,%) 27(61%)	8 (53%) 14 (64%) 7 (78%)	О Щ -10.0				O -10.0			ж		
SCr (µmol/L) 64.8 (21.4)	52.9 (16.4) 69.2 (21.4) 75.1 (19.7)	-12.0 0 2 4	6 8 10 12 14	16 18 20		-12.00	2 4 6	8 10 12 14	16 18		
Albumin \leq 34 g/L (n,%) 31 (70%)	14 (93%) 15 (68%) 4 (44%)	Measured F	ree Phenytoin Concentration	ı (µmol/L)		Me	easured Free Ph	enytoin Concentration (µ	mol/L)		
		D		Drovinsial							
Fracerhealt	h Vancouver	Trovidence	5	Provincial	Health	1					
	CoastalHealth	HEALTH CARE	E i	Province-wide	e solution	ւy Տ.					
Better health. Best in health c	are. Promoting wellness. Ensuring care.	How you want to be	e treated.	Better health	۱.						





Table 4: Bias and Precision for Subgroups based on CYP interaction, dose, eGFR											
MPE (µmol/L)/ RMSE (95% CI)	Equation 1	Equation	2	Equ	ation 3	Equation 4	Equatio	on 5	Equ	ation 6	
CYP interaction	0.8 (0.0 to 1.6)	-2.8 (-4.6 to (n=13)	-1.0)	-1.4 (-3.2 to 0.4) (n=13)		-1.3 (-2.3 to-0.3)	-1.3 (-2.3 to-0.3)		-1.1 (-2.0 to -0.2)		
(n= 19)	2.0 (-0.2 to 4.2)	4.2 (-14.8 to (n=13)	23.2)	3.5	(-9.6 to 16.6) <i>(n=13)</i>	2.5 (-4.5 to 9.5)	2.6 (-5.2 t	o 10.4)	2.4	(-3.9 to 8.7)	
No CYP interaction	1.6 (0.9 to 2.3)	-1.0 (-1.7 to (n=17)	-0.3)	0.4 (-0.3 to 1.1) (<i>n</i> =17)		-0.6 (-1.2 to 0.0)	-1.2 (-2.2 to -0.2)		-0.3 (-0.9 to 0.3)		
(n= 25)	2.4 (-1.1 to 5.9)	1.8 (-1.2 to (n=17)	4.8)	1.6	(0.4 to 2.8) (n=17)	1.6 (-0.7 to 3.9)	2.8 (-6.6 t	o 12.2)	1.5	(-0.5 to 3.5)	
Total Daily PHT dose	1.3 (0.7 to 1.9)	-1.0 (-2.2 to 0.2) (<i>n=4</i>)		0.3 (-0.6 to 1.2) (<i>n=4</i>)		-0.5 (-1.3 to 0.3)	-0.9 (-1.8 to 0.0)		-0.3 (-1.1 to 0.5)		
<300 mg (n= 5)	1.5 (0.0 to 3.0)	1.4 (-0.9 to (n=4)	3.7)	0.8 (0.3 to 1.3) (<i>n=4</i>)		1.0 (0.2 to 1.8)	1.3 (-0.4 to 3.0)		0.8 (0.3 to 1.3)		
300 mg (n=13)	0.4 (-0.6 to 1.4)	-3.3 (-5.9 to -0.7) (<i>n=8</i>)		-2.1 (-4.4 to 0.2) (<i>n=8</i>)		-1.5 (-2.8 to -0.2)	-1.6 (-3.0 to -0.2)		-1.3 (-2.6 to 0.0)		
	1.8 (-0.5 to 4.1)	4.8 (-23.0 to 32.6) (n=8)		3.8 (-14.6 to 22.2) (<i>n=8</i>)		2.8 (-7.0 to 12.6)	3.0 (-8.5 to 14.1)		2.6 (-6.0 to 11.2)		
301-499 mg (n= 17)	1.3 (0.4 to 2.2)	-1.3 (2.5 to -0.1) (<i>n</i> =13)		0.0 (-1.4 to 1.4) (<i>n</i> =13)		-0.9 (-1.7 to -0.1)	-1.7 (-3.1 to -0.3)		-0.6 (-1.4 to 0.2)		
	2.3 (-0.3 to 4.9)	1.1 (-8.2 to 10.4) <i>(n=13)</i>		1.0 (-6.3 to 8.3) (<i>n</i> =13)		1.8 (-2.6 to 6.2)	3.3 (-10.6	o 17.2) 1.7		(-2.3 to 5.7)	
≥500 mg (n= 9)	2.4 (1.1 to 3.7)	-1.2 (-2.1 to -0.3) (<i>n=5</i>)		0.9 (-0.2 to 2.0) (<i>n=5</i>)		-0.3 (-1.3 to 0.7)	0.0 (-0.9	to 0.9) 0.0		(-1.0 to 1.0)	
	3.0 (-5.8 to 11.8)	1.5 (-0.3 to (<i>n</i> =5)	3.3)	1.4	(-0.2 to 3.0) (<i>n</i> =5)	1.5 (-0.1 to 3.1)	1.3 (0.3 t	o 2.3)	1.5	(-0.2 to 3.2)	
eGFR 30-59	1.4 (0.8 to 2.0)	N/A		N/A		-0.9 (-2.1 to 0.3)	-1.5 (-4.2 to 1.2)		-0.6 (-1.6 to 0.4)		
mL/min (n=3)	1.5 (-0.4 to 3.4)	N/A			N/A	1.2 (-1.6 to 4.0)	2.4 (-9.0 t	o 13.8)	0.9	(-0.7 to 2.5)	
60-89 mL/min (n=8)	0.8 (0.1 to 1.5)	-1.0 (-1.9 to -0.1) (<i>n=4</i>)		0.3 (-0.7 to 1.3) (<i>n=4</i>)		-0.8 (-1.4 to -0.2)	-0.5 (-1.0 to 0.0)		-0.6 (-1.2 to 0.0)		
	1.2 (0.2 to 2.2)	1.3 (-1.0 to 3.6) <i>(n=4)</i>		0.9 (0.0 to 1.8) (<i>n=4</i>)		1.2 (0.5 to 1.9)	0.8 (0.2 to 1.4)		1.0 (0.5 to 1.5)		
>90 mL/min (n= 33)	1.3 (0.6 to 2.0)	-1.9 (-3.0 to -0.8) (<i>n=25</i>)		-0.6 (-1.7 to 0.5) (<i>n</i> =25)		-0.9 (-1.6 to -0.2) -1.4 (-2.3	to -0.5)	-0.7	(-1.4 to 0.0)	
	2.5 (-0.3 to 5.3)	3.3 (-7.0 to 13.6) (<i>n=25</i>)		2.8 (-4.2 to 9.8) (<i>n</i> =25)		2.3 (-2.2 to 6.8)	3.0 (-5.3 t	3.0 (-5.3 to 11.3)		2.1 (-1.9 to 6.1)	
Table 5: P	otential for	Inappro	pria	te [Dose Cha	anges from	Predict	ive E	qua	ations	
	Actual	1		2 (n=30)	3 (<i>n=30</i>)	4	5		6		
< 4 µmol/L (n)		13	5		14	6	12 13			12	
$4 - 8 \mu \text{mol/L}(n)$		16	23		11 5	15	23 22 Q Q			23	
> 8 µmol/L (n)		15	10		5	9	9 9			9	
change in		11 (25)		14 (47)	6 (20)	11 (25)	12 (27)		11 (25)		
Results											
The Winter-Tozer equation tended to overpredict											
I ne May et al., Kane et al. (Equations 4 & 5), Haidukewych et al., and Cheng et al. equations tended to underpredict											
Limitations											
 eGFR used instead of CrCl for Equation 5 											
- GUINUSCUIIISICAU UNUNUNUNUNUNUNUNUNUNUNUNUNUNUNUNUNUNU											



Free PHT assay at VGH changed Feb 27, 2012 • 18 concentrations after this date, 26 concentrations before Small sample size

Interacting medication not at steady state

Conclusions

Overall predictive performance of currently developed equations poor In general, the Cheng et al. equation was the most precise; the Haidukewych et al. equation was the least biased Larger sample sizes required to derive new equations with reduced bias and/or increased precision

