Derivation and Validation of an Equation to Predict Free Valproate Concentration in Intensive Care Patients

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Background

- Valproate (VPA) is highly protein-bound to albumin, with the biologically active free (unbound) fraction expected to be 5-10% of the total concentration.
- Protein binding of valproate varies among intensive care unit (ICU) patients, altering the biologically active free VPA concentration.
- Free VPA concentration is measured at few laboratories and is often discordant with total VPA concentration.
- Existing equation models to predict free VPA concentration are either not validated or are inaccurate in ICU patients.

Objectives

- This study is designed to derive and validate a novel equation to predict free VPA concentration using data from ICU patients, and to compare its predictive performance to published equations.

Methods

Study design

- Multicenter, retrospective cohort study conducted at Maine Medical Center in Portland, ME, and Mayo Clinic in Rochester, MN.
- Consecutive patients ≥ 18 years of age with concomitant free and total VPA concentrations collected in the ICU were enrolled in the derivation cohort from 2014-2018, and the validation cohort from 2019-2022.

Data Collection

- Demographic data, medications, serum albumin, blood urea nitrogen (BUN), creatinine, bilirubin were recorded

Statistical Analysis

- A new equation to predict free VPA concentration was derived with multivariable linear regression using data from derivation cohort.
- The new equation and the five previously published equations were validated using clinical data from the validation cohort.
- Predicted free and measured VPA concentrations were compared with correlation, modified Bland-Altman plots, and therapeutic concordance.
- Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 4.0.3 (R Core Team, Vienna, Austria).

Results

Table 1. Patient demographics

	Derivation (n=115)	Validation (n=147)	p value
Age, years	55 (42, 68)	62 (48, 68)	0.12
Male, no. (%)	79 (69%)	93 (63%)	0.43
Weight, kg	80 (67, 98)	84 (69, 102)	0.49
Race, no (%)			< 0.001
White	98 (85%)	131 (89%)	
Other	17 (15%)	11 (8%)	
Unknown	0 (0%)	5 (3%)	
Hospital stay, days	11 (7, 29)	14 (7, 30)	0.64
APACHE score			
APACHE III (Mayo)	64 (48, 113)	92 (67, 112)	< 0.001
APACHE IV (MMC)	62 (31, 80)	56 (50, 80)	0.31
Charlson comorbidity index	5 (2, 8)	4 (2, 7)	0.89
ICU type, no (%)			0.008
Neuroscience	61 (53%)	48 (33%)	
Medical	40 (35%)	76 (52%)	
Surgical/Trauma	11 (10%)	15 (10%)	
Cardiac	3 (3%)	8 (5%)	
Free VPA concentration, mcg/mL	12 (8, 22)	13 (8, 23)	0.77
Total VPA concentration, mcg/mL	52 (36, 66)	54 (26, 71)	0.30
VPA free fraction, (%)	26.8 % (19.6, 37.8%)	24.2% (19.2, 34.3)	0.26
Normal free fraction 5-10%, no. (%)	3 (3%)	3 (2%)	0.76
Concomitant medication, n (%)			
Propofol	25 (22%)	55 (37%)	0.006
Aspirin	23 (20%)	31 (21%)	0.83
Intravenous fat emulsion	1 (1%)	3 (2%)	0.80
Clevidipine	0 (0%)	2 (1%)	0.21
NSAIDs (ketorolac, ibuprofen)	2 (2%)	2 (1%)	0.90
Laboratory values			
Creatinine (mg/dL)	0.8 (0.7, 1.2)	0.9 (0.7, 1.4)	0.36
Blood urea nitrogen (mg/dL)	17 (12, 28)	19 (12, 28)	0.17
Albumin (g/dL)	3.2 (2.6, 3.6)	3.1 (2.7, 3.6)	0.64
Total bilirubin (mg/dL)	0.3 (0.2, 0.5)	0.4 (0.2, 0.6)	0.099

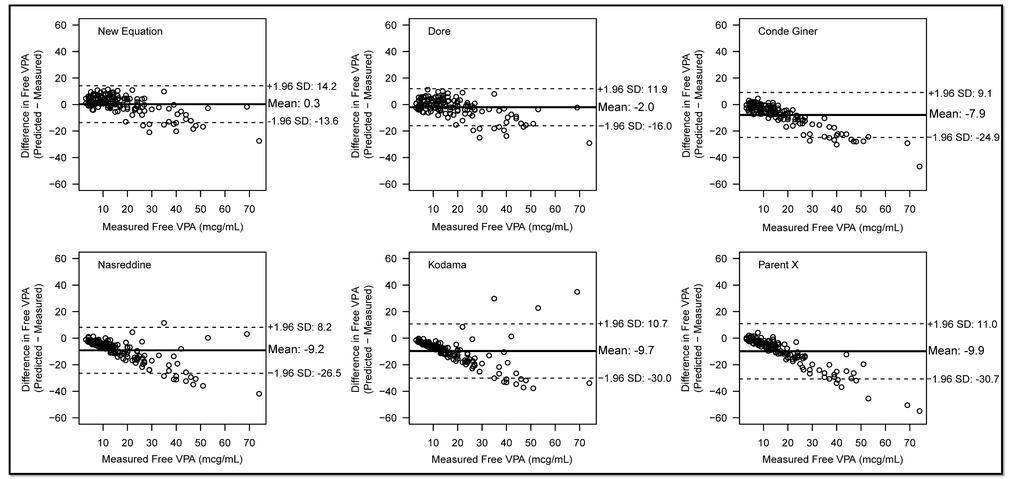
Table 1. Continuous data are reported as median (IQR) and categorical data as number (%)

Table 2. Comparison of predicted free VPA concentration to measured values for six equations among 147 ICU patients

	New Equation 2023	Parent 1993	Kodama 1993	Dore 2017	Nasreddine 2018	Conde Giner 2021
Therapeutic Comparison						
Correlation	0.85	0.67	0.68	0.85	0.75	0.84
Bias (95% Limits of Agreement)	0.3 (-13.6 to 14.2)	-9.9 (-30.7 to 11.0)	-9.7 (-30.0 to 10.7)	-2.0 (-16.0 to 11.9)	-9.2 (-26.5 to 8.2)	-7.9 (-24.9 to 9.1)
Concordance	107 (73%)	64 (43%)	43 (29%)	108 (73%)	63 (43%)	89 (60%)
Discordance	40 (27%)	83 (57%)	104 (71%)	39 (27%)	84 (57%)	58 (40%)
Overestimation	31 (78%)	2 (2%)	0	18 (46%)	1 (1%)	3 (5%)
Underestimation*	9 (22%)	81 (98%)	104 (100%)	21 (54%)	83 (99%)	55 (95%)

Table 2. *Percentages for over- and underestimation reflect fraction of discordant patients

Figure 1. Modified Bland-Altman plots assessing the association of the difference between measured VPA concentration and predicted values for six equations



New Equation 2023:

Free VPAC (mcg/mL) = 10·74 + 0·34*(total VPAC [mcg/mL]) – 4·60*(albumin [g/dL]) + 0·02*(BUN [mg/dL]) + 2·14*(if propofol = yes) + 1·51*(if aspirin = yes)

Conclusion

- For patients at risk of altered protein binding such as ICU patients, most published equations to predict free VPA concentration are discordant with measured free VPA concentration.
- The inclusion of aspirin, propofol, and BUN adjustments in a new equation did not result in improved predictive performance compared to the Dore equation which accounts for total VPAC and albumin.
- External validation is needed to confirm its applicability and improve its precision. Until these data are available, measuring the free VPA concentration during critical illness is recommended.

References/Acknowledgement

- All authors declare no conflict of interests.

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