Clinical Pharmacokinetic Monitoring of Free Valproic Acid Levels: A Systematic Review

Kevin Lin, PharmD (Candidate).; Vivien Cao B.Sc(Pharm)., PharmD., ACPR; Charles Au B.Sc(Pharm)., PharmD., ACPR.; Karen Dahri, B.Sc., B.Sc(Pharm)., PharmD., ACPR.

Background

- Current guidelines recommend therapeutic drug monitoring as a critical component of valproic acid (VPA) therapy with total levels commonly adopted[1-2]
- Due to high protein-binding and saturable binding characteristics, the active unbound (or free) portion of serum VPA can be misrepresented by total VPA serum levels in certain clinical scenarios

Objectives

- To identify an optimal therapeutic range for free VPA levels
- To explore correlation of free levels to clinical toxicity and therapeutic benefit
- To describe clinical situations warranting use of free VPA levels by examining predictors of discordance or concordance between free and total VPA levels

Methods

- Population: Any patient taking VPA for any indication that included free VPA serum level monitoring were included
- Inclusion: Randomized controlled trials, observational studies, case series and case reports published prior to the year June 20, 2021
- Exclusion: Reviews, guidelines, animal studies, editorials, letters, commentaries.
- Data collection: Data included study design, VPA use, patient characteristics, pharmacokinetic parameters, free and total VPA levels, and adverse effects
- Risk of bias and quality assessment: Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool; CAre REport (CARE) checklist and a tool proposed by Murad et al[3] assessed case studies
- Two authors reviewed studies independently. Any discrepancies were resolved with the use of a third and fourth reviewer

Results

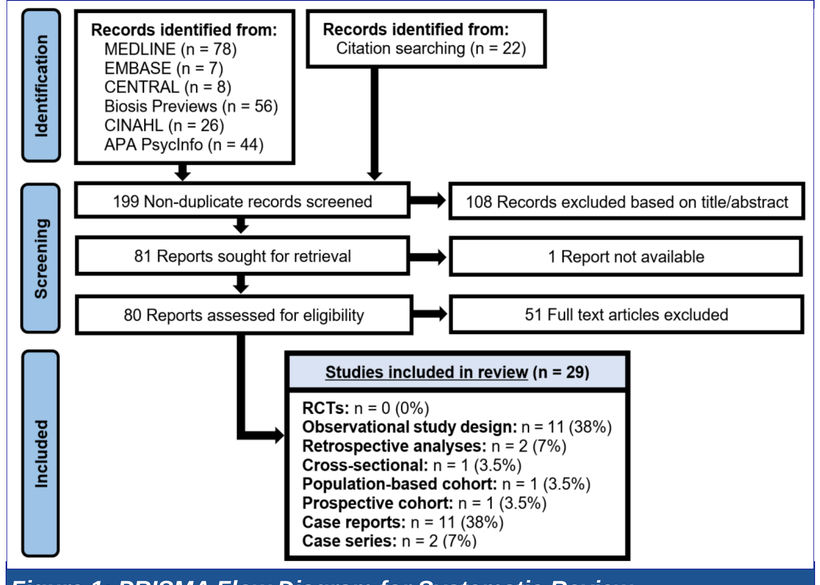

Figure 1: PRISMA Flow Diagram for Systematic Review

Table 1: Summary of Observational Studies and Reported Free VPA Therapeutic Ranges

Author	Design	N	Age Range	VPA Indication	Therapeutic Range (µmol/L)
Yu, 1984	Observational	18	1-12	▪ Epilepsy	37-410
Kilpatrick, 1987	Population-based cohort	70	16-57	▪ Epilepsy	20-50
Sriboonruang, 2011	Observational	66	18-60	▪ Psychiatric conditions	27.7-83.2
Gibbs, 2015	Cross-sectional	257	49.1[a] 33.1[b]	▪ Epilepsy	26.3-609.8

[a]Mean age of inpatient group; [b]Mean age of outpatient group

Table 2. Summary of Observational Studies and Associated Adverse Events

Author	Design	N	Age Range	VPA Indication	Adverse Event (Incidence)	Free VPA Cut-off Value (µmol/L)	AUC-ROC [95% CI]
Cramer, 1986	Observational	57	23[a] 29[b]	▪ Epilepsy	▪ Neurologic symptoms	207.9	-
Itoh, 2012	Retrospective analysis	19	0-28	▪ Epilepsy	▪ Hyperammonemia (15.7%)[c]	60	▪ (r_s = 0.58, p = 0.00041)[d]
Doré, 2017	Retrospective analysis	41	27-85	▪ Epilepsy (41.5%) ▪ Psychiatric conditions (58.5%)	▪ Neurologic symptoms (70.7%)[e]	70	▪ 0.78 [0.629–0.923, p = 0.007]
Tseng, 2020	Prospective cohort	51	25-96	▪ Epilepsy (99%) ▪ Post-Herpetic Neuralgia (1%)	▪ Hyperammonemia (31.6%)[c]	61.7	▪ NSS
					▪ Thrombocytopenia (27.6%)[e]	103.2	▪ 0.77 [0.66–0.88, p < 0.001]
					▪ Hepatotoxicity (4%)[f]	132.4	▪ NSS

AUC-ROC: Area Under the Receiver Operating Characteristic curve
[a]Mean age of VPA monotherapy group; [b]Mean age of VPA combination therapy group; [c]Ammonia >60 µmol/L; [d]Spearmans rank correlation determined by CART analysis; [d]Somnolence (66%), psychomotor slowing (59%), lethargy (59%), tremors (41%), confusion (38%), and encephalopathy (38%) were the most frequent symptoms; [e]Platelet count <140,000 cells/mm^3; [f]Alanine Aminotransferase >3 times upper normal limit

Table 3: ROBINS-I Tool for Non-Randomized Studies

Domain	Low	Moderate	Serious	Critical	No Information
Bias Due to Confounding	1	4	10	0	1
Bias Due to Selection	9	3	4	0	0
Bias Due to Classification	9	5	2	0	0
Bias Due to Deviations	7	5	2	0	2
Bias Due to Missing Data	12	0	3	0	1
Bias Due to Measurement of Outcomes	5	4	7	0	0
Bias Due to Selection of the Reported Result	3	5	8	0	0
n = 16					

Low Risk of Bias **Moderate Risk of Bias** **Serious Risk of Bias** **Critical Risk of Bias**

Discussion

- Epilepsy (69%) was the most common indication for receiving VPA therapy
- Four studies (Table 2) described an upper limit for free VPA levels, ranging between 60-207.9 µmol/L, but did not integrate therapeutic efficacy to identify and optimal therapeutic range
- Of the 9 observational studies reporting on therapeutic discordance; advanced age (33.3%), hypoalbuminemia (22.2%), pregnancy (11.1%), and VPA doses above 3000 mg per day (11.1%) were identified as predictors of discordance
- Of the 13 case studies reporting on therapeutic discordance, the most common predictors of discordance were hypoalbuminemia (69.2%), aspirin drug interaction (30.8%) and elevated serum free fatty acids (15.3%)
- CNS toxicity (ataxia, tremor, and/or cognitive dysfunction) was the most commonly observed adverse effect in case studies (69.2%)

Limitations

- Overall, low-quality studies retrieved with heterogeneity in the data observed
- Twelve studies (41.3%) were published prior to the year 2000
- Only 1 observational study exclusively reported on a pediatric population, limiting our ability to conduct predefined subgroup analyses
- Thirteen studies (44.8%) included were either case series or case reports

Conclusions

- In the presence of hypoalbuminemia, total VPA levels may not reflect free VPA levels
- Further high-quality trials are needed to validate an optimal therapeutic range for free VPA levels and establish guidelines for its utility in clinical practice

References

1. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs best practice guidelines for therapeutic drug monitoring: A position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008 Jul;49(7):1239–76.
2. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1/02):9–62.
3. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ evidence-based medicine. 2018;23(2):60–3.