

Misleading valproate dose-related reference ranges calculated by AGNP consensus guidelines 2017

Short running title: Valproate AGNP dose-related reference range

G Hefner^{1*}, M Hahn², M Buenger² and SC Roll²

¹Psychiatric Hospital, Vitos Klinik Hochtaunus, Friedrichsdorf, Germany

²Psychiatric Hospital, Vitos Klinik Eichberg, Eltville, Germany

Abstract

AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology 2017 were recently published. In particular, definition and calculation of drug dose-related reference ranges (DRRR) were updated. However, calculation of DRRR with newly published dose-related concentration factors (DRC) for valproate lead to misleading, too high DRRR. Future pharmacokinetic studies that strongly control for confounding factors that may impact the pharmacokinetics of valproate were needed to receive appropriate pharmacokinetic data for the calculation of DRRR of valproate. We suggest for the next consensus update a DRCmean of approximately 52 ng/mL/mg. Thus, an approximately 50% reduction in DRCmean is recommended, as the DRCmean in the 2017 guidelines amounts 98.5 ng/mL/mg. Currently, DRRR of valproate should be used with caution in clinical practice.

Letter to the editor

Recently, the Therapeutic Drug Monitoring (TDM) task force of the working group on neuropsychopharmacology and pharmacopsychiatry (AGNP) issued actualized Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017 [1]. In particular, definition and calculation of drug dose-related reference ranges (DRRR) [2] were updated. While the 2011 guidelines [3] list dose-related plasma concentration factors (C/D) for the calculation of DRRR, new guidelines 2017 [1] list dose-related concentration factors (DRC). In the guidelines 2011 [3], C/D_{low} and C/D_{high} factors were multiplied by the daily dose for the calculation of DRRR. After the update [1], these factors were replaced by DRC_{low} and DRC_{high} .

In the 2011 guidelines [3], C/D factors for valproate were only given for a dosing interval of 24h, while the new guidelines [1] additionally list DRC factors for a dosing interval of 12h. Furthermore, as presented in the updated guidelines, the new calculation of DRC factors considered the short elimination half-life of valproate, that should lead to more reliable DRRR [1].

Pharmacokinetic data for the calculation of C/D factors (2011 guidelines [3]) were based on only one pharmacokinetic study [3]. The updated guidelines, based on most evident literature, added one further study for the calculation of DRC factors [1].

Overall, the DRRR calculation was further ameliorated in the guidelines 2017 [1] and therefore, a more suitable valproate DRRR was expected for clinical practice. Nevertheless, Hefner and colleagues detected very similar misleading results for calculated valproate DRRR 2017 compared with the 2011 guidelines [4].

In this retrospective study by Hefner et al. [4], calculated DRRR of the guidelines 2011 [3] and 2017 [1] were compared with individual valproate serum concentrations of 26 psychiatric inpatients. Included

patients had a mean±standard deviation (SD) age of 45±12 years (23-63 years) and received by mean±SD 1537±596 mg (600-2600 mg) valproate. Mean±SD valproate serum concentration was 70.3±19.0 µg/mL (30.5-114.0 µg/mL), mean±SD valproate C/D 52.3±24.7 ng/mL/mg (25.0-107.2 ng/mL/mg).

As only patients without pharmacokinetic abnormalities (e.g. liver or kidney disease, age ≥65 years) that were adherent to medication (dosing interval 12h) were included in the study, reliable results were expected [4].

However, most valproic acid serum concentrations of "normal" psychiatric inpatients (n=26) were not, as expected, within, but below the calculated DRRR in the 2017 guidelines (65.4%, n=17) guidelines, similar to the 2011 guidelines (76.9%, n=20). None serum level was above the DRRR [4].

C/D factors of the guidelines 2011 [3] and DRC factors (dosing interval 12h) of the updated guidelines [1] do not differ markedly (C/D_{low} : 71.23, C/D_{high} : 154.32 ng/mL/mg vs. DRC_{low} : 62.2, DRC_{high} : 134.8 ng/mL/mg). This similarity could explain that only marginal differences in calculated DRRR could be detected by Hefner and colleagues [4].

The result of the study by Hefner et al. [4] may be explained by inconsistent pharmacokinetic data taken for the calculation of C/D and DRC factors.

Correspondence to: Gudrun Hefner, Vitos Klinik Hochtaunus, Emil-Sioli-Weg 1-3 61081 Friedrichsdorf, Germany, Tel: +49 (0)6123 - 602 - 7686 , Fax: +49 (0)6123 - 602 - 666, E-Mail: Gudrun.Hefner@vitos-rheingau.de

Key words: aAGNP consensus guidelines, Dose-related reference range, Serum concentration, Therapeutic Drug Monitoring, Valproate

Received: February 14, 2018; **Accepted:** March 27, 2018; **Published:** April 02, 2018

C/D factors of the 2011 guidelines [3] were solely based on data obtained from a pharmacokinetic study by Vasudev and colleagues [5]. Small sample size (n=9) of patients with bipolar disorder limited the power of this study. DRC factors [1] of the 2017 guidelines were also based on data of this small study [5], and additionally on data of Chu and colleagues [6]. These authors investigated the influence of genetic polymorphisms on the pharmacokinetics of valproic acid in Chinese epilepsy patients (n=225). The authors detected that allelic distribution in these patients differed significantly from that in a control group [6]. Results of both studies [5,6] were limited for the calculation of C/D and DRC factors, as patients with pharmacokinetic abnormalities were not strictly excluded from analysis.

Thus, calculating DRRR with the C/D or DRC factors could not lead to ranges that would be expected in “normal” patients, as specified in the guidelines [1,3]. In contrast, Chu et al. [6] intentionally examined the influence of a pharmacokinetic peculiarity and resulting data were therefore not suitable for the updated guidelines. Selection bias may have occurred, leading to confounding pharmacokinetic values. Johannessen Landmark and colleagues detected a 10-fold pharmacokinetic variability in valproate C/D for doses <700mg/day in women of childbearing age. The variability decreased with increasing dose to 4-fold for doses ≥1500mg/day [7]. Because of this large interindividual variability in C/D, valproate serum concentrations should be obtained in strongly selected patients without pharmacokinetic abnormalities to receive reliable pharmacokinetic data, as much lower interindividual variabilities were given in these patients.

The study by Hefner et al. [4] obtained data from exclusively “normal” patients and more samples (n=26) were included in the study, compared with the study of Vasudev et al. (n=9) [5]. Because of these facts, data from the study by Hefner and colleagues [4] seem to be more reliable for clinical practice, and future clinical studies should obtain pharmacokinetic data from “normal” psychiatric patients in an adequate sample-size.

Lastly, two different half-lives were stated in the new guidelines [1]. In the section “Mood stabilizing drugs” of table 4, a valproate half-life of 11-17h is given, in the section “Anticonvulsant drug” of table 4, a half-life of 17-30h. However, as given in table 5, DRC factors have been calculated with a half-life of 14h, as detected by Vasudev et al. [5].

As no area under the concentration curve (AUC) values were available, no new DRC of valproate could be calculated from the data of Hefner and colleagues [4]. Nevertheless, based on calculated C/D, we recommend for the next consensus update a DRC_{mean} of approximately

52 ng/mL/mg. Thus, an approximately 50% reduction in DRC_{mean} is recommended for the next update, as the DRC_{mean} in the 2017 guidelines amounts 98.5 ng/mL/mg.

Finally, the DRRR calculation was further ameliorated in the guidelines 2017 [1], but the validity of factors (DRC) to calculate DRRR of valproate (dosing interval 12h) seems to have not improved. Therefore, DRRR of valproate should be used with caution in clinical practice. Future studies are necessary that analyze pharmacokinetic data of valproate in carefully selected “normal” patients [1] and strongly control for confounding factors that may have an influence on the pharmacokinetics of valproate. TDM should be conducted to titrate the patient within the therapeutic reference range of valproate [1].

Acknowledgements

None

Conflicts of interests

Gudrun Hefner is a co-author of the new published AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. She reports no conflict of interest with this publication. All other authors declare no conflicts of interest as well.

References

1. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, et al. (2017) Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. *Pharmacopsychiatry* 51: 9-62. doi: 10.1055/s-0043-116492 [Crossref]
2. Haen E, Greiner C, Bader W (2008) Expanding therapeutic reference ranges using dose-related reference ranges. *Nervenarzt* 79: 558-566.
3. Hiemke C, Baumann P, Bergemann N, Conca A, Dietmaier O, et al. (2011) AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry* 44: 195-235. [Crossref]
4. Hefner G, Hahn M, Buenger M, Sibylle C Roll. (2017) Comparison of Dose-Related Reference Ranges with Individual Psychotropic Drug Serum Concentrations in Clinical Practice – AGNP Consensus Guidelines 2011 and 2017. *J Pharmacol Pharm Res* 1: 001.
5. Vasudev K, Das S, Goswami U, Tayal G (2001) Pharmacokinetics of valproic acid in patients with bipolar disorder. *J Psychopharmacol* 15: 187-190. [Crossref]
6. Chu XM, Zhang LF, Wang GJ, Zhang SN, Zhou JH, et al. (2012) Influence of UDP-glucuronosyltransferase polymorphisms on valproic acid pharmacokinetics in Chinese epilepsy patients. *Eur J Clin Pharmacol* 68: 1395-1401. [Crossref]
7. Landmark JC, Burns ML, Baftiu A, Farnen AH, Lossius MI, et al. (2017) Pharmacokinetic variability of valproate in women of childbearing age. *Epilepsia* 58: e142-e146. [Crossref]