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Comparison of Dose-Related Reference Ranges with Individual Psychotropic Drug Serum Concentrations in Clinical Practice – AGNP Consensus Guidelines 2011 and 2017

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Abstract

Introduction: In 2017, AGNP Consensus Guidelines were updated with special focus on improved dose-related reference ranges (DRRR). DRRR can be used to identify pharmacokinetic abnormalities in individuals by comparing the expected calculated range with a measured drug concentration. We compared DRRR of the consensus guidelines 2011 and 2017 with drug concentrations in psychiatric patients.

Materials and Methods: Data of 236 psychiatric inpatients whose drug serum concentrations had been measured were retrospectively screened and strongly selected to receive data from "normal" patients without pharmacokinetic abnormalities. For about 68% of the drug concentrations of these patients should be within a valid calculated DRRR. DRRR were calculated according to 2011 and 2017 guidelines.

Results: In total, 78 drug concentrations from 71 patients were available for analysis. Only 33.3% (n=26) of these concentrations were within the DRRR 2011 and 47.4% (n=37) within the DRRR 2017. The validity of calculated DRRR could only be confirmed for venlafaxine in the new guidelines, as 77.8% (n=14) of drug concentrations were between the DRRR, but not be confirmed for duloxetine (n=9) and valproic acid (n=26).

Discussion: The DRRR calculation in the guidelines 2017 was notably improved but further pharmacokinetic data is needed to allow a better "forecast" of the expected drug concentrations in a patient though, allowing a future guideline update to generate more accurate factors for the DRRR calculation. Currently, DRRR can support clinical decision making, but they should be used with caution for several drugs as a rough orienting range.

Keywords: AGNP consensus guidelines; Dose-related reference range; Serum concentration; Therapeutic drug monitoring; Psychiatry; Psychotropic drug

Introduction

In September 2017, the Therapeutic Drug Monitoring (TDM) task force of the working group on neuropsychopharmacology and pharmacopsychiatry (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie, AGNP) issued new best practice guidelines for TDM in psychiatry [1]. In general, two reference ranges were important for the optimal interpretation of TDM results, the therapeutic and the dose-related reference range (DRRR). The first range is pharmacodynamic based, the second pharmacokinetic based [1].

Compared with the previous guidelines in 2011 [2], the new guidelines were updated and extended with special focus on the calculation of DRRR for psychotropic drugs, first introduced by Haen et al. [3].

The DRRR is defined in the guidelines as the mean–standard deviation (SD) to mean+SD range in which a drug blood concentration in medicated patients is expected. It contains 68% of correctly determined drug concentrations measured in "normal", adherent patients without special pharmacokinetic abnormalities (amongst others 18-65 years old, without pharmacokinetically relevant comorbidity, no genetic abnormalities in drug metabolism, no intake of cytochrome P450 inhibitors or inducers) [1,2]. Dose-related reference ranges can be used to identify pharmacokinetic abnormalities or insufficient adherence, comparing a measured drug concentration in blood of an individual patient with a theoretically calculated expected drug concentration range [3,4].

The validity of the calculated DRRR in the previous guidelines was limited for several reasons, as explained in the new guidelines [1]. Derived from the original concept of Haen et al. [3] for average drug serum concentrations in the 2011 guidelines [2], the range is now defined as range under trough-level conditions [1]. Therefore, calculation of the DRRR was modified for the new update. Several new equations were given to compute the range correctly under

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different conditions as a function of the prescribed dose, dosing interval and pharmacokinetic parameters [1]. In this short report, for clinical utility, we analyzed and compared theoretically calculated DRRR of the consensus guidelines 2011 and 2017 [1,2] with individual psychotropic drug concentrations of psychiatric patients in clinical practice.

Materials and Methods

This TDM-study was a retrospective analysis based on a large Therapeutic Drug Monitoring (TDM) database of the psychiatric hospital, Vitos Klinik Eichberg, Eltville, Germany. Data were obtained from 236 inpatients who had been treated with a psychotropic drug under naturalistic conditions and for whom serum concentration of psychotropic drugs were measured. Overall, psychotropic drug serum concentrations carried out in the hospital (July 2016 to January 2017) were retrospectively assessed. Patient information, amongst others regarding smoking status, steady-state conditions and co-medication, were analyzed. Data were documented by the physician in the computerized hospital information system. Patient characteristics and the determined serum concentration were anonymized and transferred to a common TDM-database. The database contained 539 samples from 236 patients. Data were strongly selected to investigate the validity of the calculated DRRR. To receive data from "normal" patients, as defined in the guidelines, patients aged ≥ 65 years, patients <18 years of age, patients with pharmacokinetically relevant comedication for the respective drug (e.g., CYP inhibitors or inducers [1]) or comorbidities (e.g., liver or kidney-disease) were excluded from analysis. Smokers were excluded when a serum concentration of a major CYP1A2-substrate, as listed in the guidelines [1], was analyzed, as polycyclic aromatic hydrocarbons in smoke induce CYP1A2 [5]. No trough-level or steady-state conditions (5 half-lives), as defined by the guidelines [1,2], and partial/non-adherence were further exclusion criteria. Depot medication was also excluded. Missing documentation of the nurses about the intake of the drug (e.g., patient refuses to take drug) at any time during 7 days before the level was drawn was another exclusion criterion. When there were multiple measurements of a certain drug in a patient, only the most recent sample of a patient was included for the final analysis. Samples where information about dosage or drug serum concentration were lacking (e.g., because of interference with the analytical method) were also excluded. Samples were included for analysis when minimum five patient drug serum concentrations were available. Valproic acid serum concentration was quantified by chemiluminescent microparticle immunoassay (CMIA). All other psychotropic drug serum concentrations were quantified by using either a liquid chromatography-mass spectrometry (LC-MS) or liquid chromatography tandem-mass spectrometry (LC-MS/MS) method in the laboratory Bioscientia, institute for medical diagnostics GmbH, Ingelheim.

For the calculation of DRRR with the 2011 guidelines, C/D low and C/D high factors were multiplied by the daily dose [2]. For the antidepressant venlafaxine, C/D low and C/D high of the parent compound and of the active metabolite were summarized, as not specified in the guidelines 2011. For the calculation of DRRR with the 2017 guidelines [1], dose-related concentration factors (DRC) low and high were multiplied by the daily dose. Special DRC factors were given for the active moiety of drugs with active metabolites, such as venlafaxine. The 2017 calculation was made under consideration of the daily dose interval Tau [1]. Calculated DRRR of the guidelines 2011 and 2017 were compared with individual psychotropic drug serum concentrations of psychiatric inpatients in clinical practice. Referring to the guidelines 2011 and 2017 [1,2], 68% of the drug serum concentrations of the selected patients should be within the DRR.

Furthermore, in a subanalysis, smoking patients who ingested the antidepressant and selective CYP1A2 substrate duloxetine [5] were selected under the remaining exclusion criteria. Smoking induces CYP1A2 [6] and therefore decreases duloxetine serum concentration [7]. In this regard, duloxetine served exemplary as probe drug for a second test, as drug serum concentration of these patients should be below the calculated DRRR in clinical practice.

Results

In total, 78 drug serum concentrations from 71 inpatients with a mean (mean ± SD) age of 43 ± 13 years (range 19-64 years) were included in the study. Divided by psychotropic drugs, 8 aripiprazole, 9 duloxetine, 5 lamotrigine, 12 risperidone, 26 valproic acid and 18 venlafaxine serum concentrations could be included for analysis. Among all, 33.3% (n=26) of drug serum concentrations of included patients were within the DRRR 2011, 47.4% (n=37) within the DRRR 2017. Table 1 presents the results, divided by the different drugs.

In the subanalysis, 13 patients with a mean (mean ± SD) age of 49 ± 11 years (range 25-63 years) were included. Of those, 7.7% (n=1) of the duloxetine serum concentrations of smoking patients were below the DRRR 2011, 15.4% (n=2) below the DRRR 2017. Table 2 presents further results of the subanalysis.

Discussion

The topic of this study is late-breaking, as the new AGNP Consensus Guidelines were recently published at September 14, 2017. Referring to the guidelines 2011 and 2017 [1,2], around 68% of drug serum concentrations of the carefully selected patients who do not meet any exclusion criteria should be within the DRRR. To our knowledge, this TDM-study is the first that analyzed the validity of this assumption.

Under consideration of the limited sample size of this study (n=78), we analyzed that only 33.3% (n=26) of drug serum concentrations of strongly selected patients without pharmacokinetic abnormalities were within the DRRR 2011 and 47.4% (n=37) within the DRRR 2017. Referring to the guidelines 2011, only risperidone (active moiety) serum

Serum concentration of psychotropic drugs							
Drug	Below (n, %) dose-related reference range		Within (n, %) dose-related reference range		Above (n, %) dose-related reference range		In total (n, %)
	2011	2017	2011	2017	2011	2017	
Aripiprazole	1 (12.5%)	1 (12.5%)	4 (50.0%)	4 (50.0%)	3 (37.5%)	3 (37.5%)	8 (100.0%)
Duloxetine	0 (0.0%)	0 (0.0%)	1 (11.1%)	1 (11.1%)	8 (88.9%)	8 (88.9%)	9 (100.0%)
Lamotrigine	3 (60.0%)	3 (60.0%)	2 (40.0%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	5 (100.0%)
Risperidone (active moiety)	0 (0.0%)	0 (0.0%)	10 (83.3%)	7 (58.3%)	2 (16.7%)	5 (41.7%)	12 (100.0%)
Valproic acid	20 (76.9%)	17 (65.4%)	6 (23.1%)	9 (34.6%)	0 (0.0%)	0 (0.0%)	26 (100.0%)
Venlafaxine (active moiety)	15 (83.3%)	3 (16.7%)	3 (16.7%)	14 (77.8%)	0 (0.0%)	1 (5.5%)	18 (100.0%)
In total (n, %)	39 (50.0%)	24 (30.8%)	26 (33.3%)	37 (47.4%)	13 (16.7%)	17 (21.8%)	78 (100.0%)

Table 1: Psychotropic drug serum concentrations (n=78) of selected patients (n=71) without pharmacokinetic abnormalities in relation to theoretically calculated dose-related reference ranges. Referring to the guidelines 2011 and 2017 [1,2], for about 68% of the drug serum concentrations of these patients should be within the dose-related reference range.

Serum concentration of duloxetine in smokers						
Below (n, %) dose-related reference range		Within (n, %) dose-related reference range		Above (n, %) dose-related reference range		In total (n, %)
2011	2017	2011	2017	2011	2017	
1 (7.7%)	2 (15.4%)	9 (69.2%)	8 (61.5%)	3 (23.1%)	3 (23.1%)	13 (100.0%)

Table 2: Duloxetine serum concentrations of smoking patients (n=13) in relation to theoretically calculated dose-related reference ranges. Referring to the guidelines 2011 and 2017 [1,2], drug serum concentrations of these patients should be below the dose-related reference range.

concentrations were with 83.3% (n=10) within the range and therefore above the assumption of for about 68%. In the 2017 guidelines, only venlafaxine (active moiety) serum concentrations were with 77.8% (n=14) within the range and therefore above the assumed two thirds of patients.

As stated in the new guidelines [1], the validity of presented calculations was newly controlled for plausibility. Plausibility was confirmed when the empirical evaluated mean trough-level concentration was within the theoretical calculated DRRR. However, the validity could only be confirmed for venlafaxine (active moiety), but not be confirmed particularly for duloxetine and valproic acid. Therefore, the validity of calculated DRRR still seems to be not plausible for all of the published drugs.

To discuss the results of this study, the limitations of the calculation of the DRRR 2011 and the innovation of the new calculation 2017 were summarized below.

In general, TDM of psychotropic drugs is based in both guidelines [1,2] on the measurement of trough-level (time point of minimal fluctuation of drug serum concentration). However, the concept of DRRR 2011 [2] was based on average drug serum concentrations (cav) that cannot be assigned to a distinct time-point and neglects fluctuation of drug serum concentrations. Therefore, the DRRR is now defined as a trough-level (cmin) range [1] and different equations amongst others to compute expected trough-level or steady-state concentration of a drug were published.

As explained in the new guidelines [1], the equation in the 2011 guidelines for calculation of the cav is only valid and useful when the respective drug has a long elimination half-life, in relation to the dosing interval. Otherwise, when the drugs' elimination half-life is shorter than the dosing interval, calculated values were not valid and useful for clinical practice. Computed values for cmin is then more than 30% lower than for cav, as presented in the new guidelines for valproic acid [1]. Nevertheless, the results for calculated valproic acid DRRR differ only marginally between the two guidelines [1,2] in this study. Most valproic acid serum concentrations were below the calculated DRRR in the 2011 (76.9%, n=20) and 2017 (65.4%, n=17) guidelines. The result of the new guidelines may be explained by inconsistent pharmacokinetic data taken for the calculation of DRC factors. For their calculation, a half-life of 14 h was assumed. However, listed as anticonvulsant and mood-stabilizing drug, the new guidelines present two completely different half-lives of valproic acid i.e., 11 h to 17 h and 17 h to 30 h (Table 4 from Hiemke et al. [1]).

The above mentioned limitation of the guidelines 2011 [2] were also valid for a lot of other drugs particularly with a short half-life, considering the dosing interval, e.g., for venlafaxine. In this study, 83.3% (n=15) of venlafaxine serum concentrations were below the DRRR 2011.

Overall, the 2011 guidelines [2] assumed for all 83 listed neuropsychiatric drugs, except depot medication, a dosing interval of 24 h for calculation of C/D factors. As listed in the new guidelines [1], aripiprazole, which will be prescribed once daily, has a long half-life (60 h to 80 h). Therefore, the prescribed limitation is negligible for this drug which could explain that no differences between old and new guidelines [1,2] could be detected in this study. Fifty percent (n=4) of aripiprazole serum concentrations were within the DRRR 2011 and 2017. Nevertheless, all other analyzed drugs in this study possess considerably shorter half-lives which could, amongst others, explain a high number of drug serum concentrations outside the calculated DRRR.

It has to be further considered that for the calculation of

C/D factors 2011 [2], pharmacokinetic data was extracted from sparse selected studies and often included only a small number of patients, as for aripiprazole, risperidone (oral) or valproic acid (n<10), which could also explain why calculated C/D factors deliver imprecise results as shown in this analysis.

Concerning the active moiety of drugs (parent drug plus active metabolite), C/D factors in the 2011 guidelines [2] were only listed for the antipsychotic drug risperidone, and 83.3% of risperidone serum concentrations were within the DRRR 2011 [2]. Inconclusive results of venlafaxine serum concentrations (active moiety) were explainable by the fact that for the calculation of DRRR, C/D low and C/D high factors for the active moiety were not specified. Therefore, C/D low and C/D high of the parent compound and of the active metabolite were summated in this study which led to too high calculated dose-related ranges. Therefore, 83.3% (n=15) of venlafaxine serum concentrations were below the calculated DRRR 2011. Venlafaxine has a short elimination half-life of 6 h and the active metabolite O-desmethylvenlafaxine of 11 h, the metabolite-to-parent compound ratio is 2.7-7.7 [1]. Therefore, if only C/D low or C/D high of either venlafaxine or the active metabolite would have been taken into account for calculation, alternative misleading ranges would have been created.

Updated guidelines list [1] based on new equations, DRC factors for 120 drugs, for 26 with inclusion of metabolites or active moiety (e.g., venlafaxine) respectively. Based on pharmacokinetic data in the literature and recommended schedules of drug application, DRC factors are given for different time intervals between last dose and blood withdrawal. DRC factors are further based on the most evident pharmacokinetic data. Accordingly, much more pharmacokinetic references are listed in the guidelines 2017 [1]. The new created DRC factors for the active moiety of venlafaxine seem to be much more valid for application in clinical practice, as 77.8% (n=14) of venlafaxine serum concentrations were within the DRRR in this study.

Nevertheless, as for duloxetine and lamotrigine, no improvement in validity of the calculated DRRR could be detected, compared with the previous guidelines 2011 [2]. The guidelines 2017 list a broad half-life for lamotrigine of 14 h to 104 h (Table 4 from Hiemke et al. [1]) and the DRC factors were calculated with a half-life of 14 h (Table 5 from Hiemke et al. [1]). Maybe, because of the broad lamotrigine half-life range, DRC factors should be calculated with different pharmacokinetic values to receive plausible ranges. Also concerning the antidepressant duloxetine, no improvement could be detected with the new guidelines [1]. Future pharmacokinetic studies seem to be necessary to receive reliable pharmacokinetic data, as 88.9% (n=8) of the drug serum concentrations were above the dose-related ranges 2011 and 2017 [1,2]. Therefore, studies should strongly control especially the smoking status of patients and exclude smokers from analysis. In this study, duloxetine serum concentrations of smoking patients were compared with calculated DRRR. As smoking induces CYP1A2 [6], serum concentrations of the CYP1A2 substrate duloxetine should be markedly decreased [7] and therefore be below the calculated DRRR.

However, CYP1A2 inducing effect of smoke led only to a shift of duloxetine serum concentrations within the DRRR. In total, only 7.7% (n=1) of the measured duloxetine serum concentrations were below the 2011 DRRR, 15.4% (n=2) below the 2017 DRRR. Therefore, pharmacokinetic abnormality because of CYP1A2 induction could not be identified with both calculated ranges [1,2].

Relating to the number of smokers that were still within or above the DRRR, it has to be mentioned that the number of smoked cigarettes by a patient was not considered in this study, and the activity of CYP1A2 increases with the number of smoked cigarettes per day [6]. Therefore, it is possible that CYP1A2 induction was too weak for a clinically significant induction, in particular when patients smoke a low number of cigarettes per day.

Drug serum concentrations of the strongly selected patients outside the calculated DRRR 2011 and 2017 [1,2] were not only explainable by the before mentioned factors. Outliers can also be explained by the high interindividual pharmacokinetic variability of drug serum concentration due to different patient-characteristics in absorption, distribution, metabolism of drugs and excretion. Not all reasons for these differences could be considered in our naturalistic TDM-study, e.g., body weight, genetic polymorphisms and gender [8-12]. This high patient variability is also one major reason to guide drug dosing with the use of TDM [1,2].

With respect to the study design of this retrospective TDM-study, results were limited due to small sample-sizes. However, it has to be considered that patients were carefully selected to exclude pharmacokinetic abnormalities as defined by the exclusion criteria. 539 drug serum concentrations from 236 patients were available for analysis and finally, only 78 drug serum concentrations from 71 patients were included in this study.

Due to the selection process to gain valid serum concentrations, low interindividual variabilities in serum concentrations were expected, as confounding factors of pharmacokinetic nature on drug serum concentration were prevented. Therefore, strength of this study was the strong exclusion criteria of patients. Nevertheless, the selected patient samples in a TDM-study may often not be representative for the "average" patient in a standard psychiatric setting. A patient-bias was avoided by including only the most recent serum concentration of a certain drug of a patient.

It has to be further mentioned that because of the retrospective design, this TDM-study can mainly provide data of an explorative nature, as not being able to prove any causal

relationship. Thus, results were at most descriptive and have to be interpreted with caution.

Future, prospective pharmacokinetic studies with a large number of "normal" patients are necessary to investigate the plausibility of the DRRRs of all the listed 120 drugs in a naturalistic, clinical setting.

Conclusions

The concept of the DRRR is a valuable approach and improved psychopharmacotherapy of many patients in the past [4]. This concept was further ameliorated in the new guidelines [1], as some limitations of the previous concept have been eliminated. In particular, calculation of DRRR from drugs with a short half-life or with active metabolites should be theoretically more valid with the new published data. Nevertheless, validity of calculated DRRR seems to have not generally improved, but only for several drugs, as venlafaxine (active moiety). However, future pharmacokinetic studies with a high number of "normal" patients were necessary to confirm the validity of the DRRR 2017 of the listed 120 drugs [1] in a naturalistic setting. Finally, complex assessment of drug serum concentrations with calculated DRRR gained further in quality with the new guidelines and subsequent clinical decision making, but also needs further improvement for some drugs in the future to allow better "forecasts" of the expected serum concentration in a patient. Currently, DRRR can support clinical decision making, but they should be used with caution as a rough orienting range. It does not substitute direct patient communication and clinicians should primarily focus on well-established therapeutic reference ranges [1].

Conflicts of Interests

Gudrun Hefner is a co-author of the newly 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.

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