The dose-related reference range - a new approach with improved predictive quality

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Background: For effective therapeutic drug monitoring (TDM), an individual interpretation of the drug concentration regarding to the therapeutic and dose-related reference range (DRR) is essential. Three calculation methods for DRR in normal patients have been proposed to date: cav according to Haen 2008, cmin according to AGNP TDM guidelines 2017 and cmin according to Haen 2018. All methods have different disadvantages. An evaluation of the methods regarding to the predictive quality has not yet been carried out.
The aim was to further develop the methodology and to compare all methods in terms of predictive quality of the trough levels in steady state of amlodipine, bisoprolol, metoprolol, hydrochlorothiazide and ramipril/ramiprilate.

Methods: The developed method, Cmin,R2019, is based on the Bateman function and takes into account the total available and suitable literature of the pharmacokinetics of the mentioned substances. The visualization of the drug concentration curves was realized with SigmaPlot. The predictive quality regarding to published trough levels was determined.

Results: Cmin,R2019 enables the visualization of the drug concentration curves with regard to the dosage form, variable dosages, dosage intervals (τ) and specific patient groups. Cmin,R2019 showed a lower bias as well as an improved precision in the prediction of trough levels in steady state compared to the other three methods.

Conclusion: The new procedure offers an improved overall predictive quality compared to the methods presented so far. The visual representation of the drug concentration curves is helpful for the interpretation of the measured values, especially if the blood collection did not take place in the trough level. The new method should be applied to other drugs and the predictive quality of the various methods should be compared.

Key Words: therapeutic drug monitoring, dose-related reference range, Bateman function, pharmacokinetics