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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 et al.(1), Cmin according to Hiemke et al.(2), as well as Cmin according to Klein and Haen(3). All methods have different disadvantages and 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 the antihypertensives most frequently prescribed in psychiatry: amlodipine, bisoprolol, metoprolol, hydrochlorothiazide (HCT) and ramipril/ramiprilat(4) in normal patients at different dosages and dosing intervals. The further developed methodology should be called DRR.R2019.

Methods:

A literature review of the pharmacokinetic parameters (pkps) of the drugs was conducted in pubmed and Embase. Pkps were recorded by publication and grouped by antihypertensive substance, dosage, dosing interval and where applicable by age, renal function, metabolic phenotype or pharmaceutical form. Weighted mean values and standard deviations of the pkps were calculated within the groups. The weighting factor was the number of subjects investigated in the study. If applicable linear pharmacokinetics were taken into consideration. Based on $C_{ss,min} = \frac{F \cdot D}{V} \cdot \left(\frac{ka}{ka-k}\right) \cdot \left(\left(\frac{e^{-k \cdot \tau}}{1-e^{-k \cdot \tau}}\right) - \left(\frac{e^{-ka \cdot \tau}}{1-e^{-ka \cdot \tau}}\right)\right)$(5) DRRs were calculated.

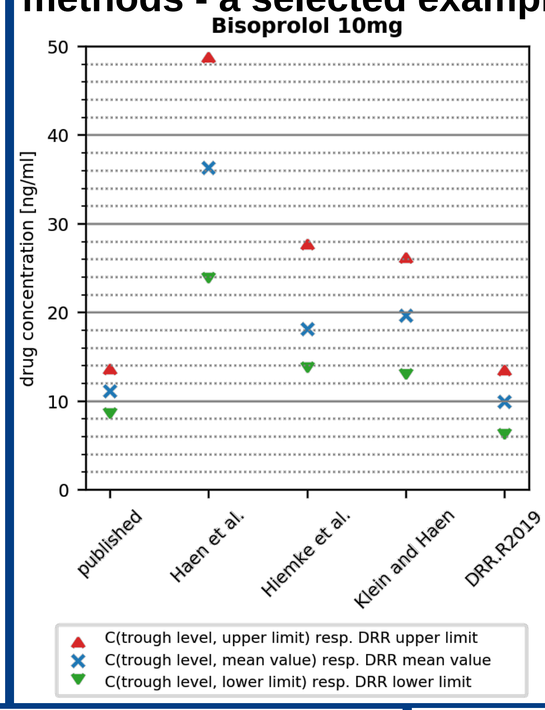
We also calculated DRRs according to the former published methods. The predictive performance according to Sheiner and Beal(6) of the different calculation methods with respect to published trough levels in steady state was determined and compared. The visualization of active ingredient concentration curves was realized with a self-programmed and validated software in which a formula based on the Bateman function(5) was used.

Results:

Results in numbers

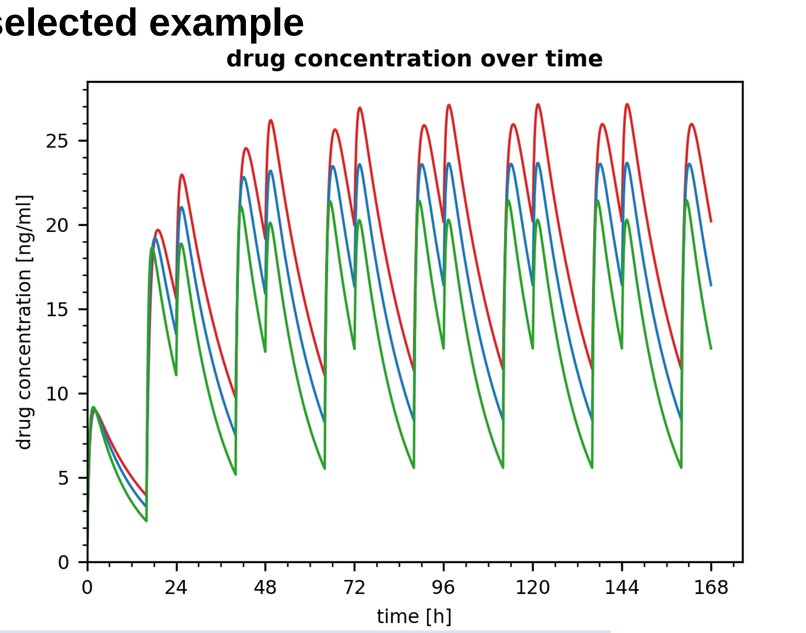
Drug substance:	Amlodipine	Bisoprolol	HCT	Metoprolol	Ramipril	Ramiprilat	Sum
Total number of references	138	74	158	294	61	(61)	**695**
Included references	71	25	75	121	34	(34)	**319**
Generated data recores	102	36	112	229	40	49	**568**
Total number of probands	2162	397	1849	2418	557	648	**8031**
Generated pkp-groups	8	5	13	32	12	13	**83**
Calculated DRRs according to DRR.R2019	7	5	12	26	10	10	**70**
thereof in nomal patients	5	5	7	21	3	3	**44**
Comparison of trough level and DRR	5	1	9	20	6	6	**47**
thereof in nomal patients	4	1	6	18	2	2	**33**

Comparison of published trough levels with the DRRs according to the different methods - a selected example



People with a normal drug concentration could be rated as noncompliant in this example if the DRRs according to Haen et al., Hiemke et al. or Klein and Haen were used to interpret the patients drug concentration

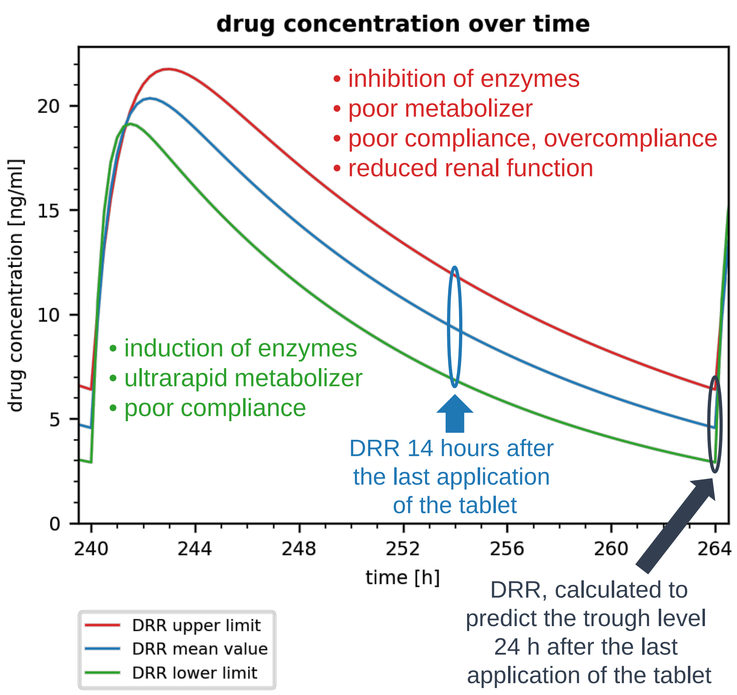
Visualization of concentration curves – a selected example



Drug concentration curve according to DRR.R2019 simulating the application of Bisoprolol 2.5 mg in the morning and Bisoprolol 5 mg 16 hours later in the evening

Interpretation of the measured drug concentration by means of the visualized drug concentration curve

Example: application of Bisoprolol 5 mg in the evening over more than 10 days



1. How many hours before taking the blood sample did the patient take the tablet? E.g. **14 hours**
2. Is the measured concentration of the active substance in the DRR, i.e. between the green and red lines?

yes - the patient builds up dose-corresponding concentrations of the active substance - everything is ok

no - the concentration of the active substance is above the red limit - see diagram for possible explanations

no - the concentration of the active ingredient is below the green limit - see diagram for possible explanations

Predictive Performance of trough levels in normal patients

Aggregation of the comparison of trough levels and DRRs in 33 pkp-groups

Prediction of:	Bias				Precision			
	Haen et al.	Hiemke et al.	Klein and Haen	DRR.R2019	Haen et al.	Hiemke et al.	Klein and Haen	DRR.R2019
C(trough level, upper limit)	100.66	67.08	-10.04	1.63	17539.81	36396.03	2020.33	307.34
C(trough level, mean value)	92.72	11.72	1.86	0.89	14603.97	4866.81	690.54	110.45
C(trough level, lower limit)	83.68	20.92	12.66	1.63	12644.74	4371.09	649.28	99.31

p < 0.05; statistically significant difference between the compared methods regarding the systematic error (bias)

p < 0.05; statistically significant difference between the compared methods regarding the absolute error (precision)

The method with the best precision (smallest value) should be preferred.

Conclusion:

☑ **Improved predictive quality compared to the methods presented so far**

☑ **Visual presentation of the active ingredient concentration curves supports the interpretation of the measured values**

→ **Application of the method DRR.R2019 to other groups of drugs and comparison of the different methods with regard to predictive performance**

References:

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(4) Endres et al. (2018): Bedeutung der Antihypertensiva bei der medikamentösen Behandlung psychisch kranker Patienten. Poster DGPPN-Kongress 2018, Berlin
(5) Langguth, Fricker, Wunderli-Allenspach (2004): Biopharmazie. Weinheim: Wiley, 1. Auflage S. 154
(6) Sheiner, Beal (1981): Some suggestions for measuring predictive performance. In: Journal of Pharmacokinetics and Biopharmaceutics 9 (4), S. 503–512

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