

Supplementary Materials

**Assessing adherence to antihypertensive medication
by means of dose-dependent reference plasma
concentration ranges and ultra-high performance
liquid chromatography-ion trap mass spectrometry
analysis**

Lea Wagmann, Aline C. Vollmer, Lucas Lauder, Felix Mahfoud and Markus R. Meyer

Table S1. Parameters of three different, freshly prepared calibrations acquired during validation procedure (slope, intercept, and deviation of back-calculated concentrations of calibrators, Cal 1-6, %, values outside the EMA guideline limits [30] are marked with an asterisk).

Analyte	Slope	Y-axis intercept	Deviation of back-calculated concentrations, %					
			Cal 1	Cal 2	Cal 3	Cal 4	Cal 5	Cal 6
Amlodipine	0.012	-0.094	-2	+7	-4	-4	0	+3
	0.010	0.003	0	-19*	+1	-4	-1	+2
	0.015	-0.035	0	-1	0	+3	+20*	-1
Bisoprolol	0.034	0.059	+1	+11	+4	-4	+2	+1
	0.022	0.014	0	0	+6	-7	+3	-1
	0.035	0.037	0	-4	+1	-9	+9	+4
Candesartan	0.011	0.040	-1	+7	+4	0	-4	-5
	0.009	0.016	0	+1	0	0	-3	+3
	0.010	0.007	0	+3	+4	-4	-2	0
Canrenone	0.034	0.57	0	+8	+1	-22*	-3	-5
	0.037	0.19	0	-5	+7	-10	+1	+8
	0.049	0.39	0	-3	+8	-7	0	+4
Carvedilol	0.066	0.15	0	+7	0	-8	-9	-11
	0.070	0.060	0	+5	-3	-1	-4	+4
	0.087	0.047	+1	-11	-1	+5	+4	+3
Metoprolol	0.016	0.038	0	0	+5	-7	+1	+1
	0.009	0.024	0	+2	+1	-2	+2	-3
	0.019	0.053	0	-5	0	-6	+7	+4
Olmesartan	0.021	0.11	-7	+15	+8	-7	+41*	-1
	0.019	0.057	+1	+2	-1	-7	-1	+6
	0.019	0.090	+3	-7	+4	-6	+3	+1
Torasemide	0.026	0.27	-18	0	+11	-2	+2	-1
	0.019	0.16	-5	-1	+10	-1	-7	+4
	0.026	0.14	-16	-4	+5	-16*	+7	-4
Valsartan	0.042	0.38	0	+37*	+4	-3	0	0
	0.047	-0.016	+5	-5	+10	-11	-3	+8
	0.050	0.21	+5	+2	-4	-12	0	+9

Table S2. Summary of the pharmacokinetic data (elimination half-life $t_{1/2}$, peak plasma concentration C_{max} , and time when C_{max} was reached, t_{max}) used for calculating the dose-dependent reference plasma concentration ranges.

Analyte	Dose, mg	$t_{1/2}$, h [33]	C_{max} , ng/mL [33]	t_{max} , h [33]
Bisoprolol	5	7	21	2
	10	7	52	2
Candesartan	8	8	61	4
	16	8	120	4
	32	8	260	4
Canrenone	100	13	600	2
Carvedilol	12.5	4	58	1
Metoprolol	50	2.5	72	1
	100	2.5	140	2
Olmesartan	20	6	390	2
	40	6	830	2
Torasemide	10	2	1,600	1
Valsartan	320	4	11,000	3

Table S3. Example calculation of the lower limit ($C_{\min-20\%}$) of the reference plasma concentration range for 10 mg bisoprolol daily. Elimination half-life $t_{1/2}$, peak plasma concentration C_{\max} , and time when C_{\max} was reached, t_{\max} , taken from Baselt [33].

Bisoprolol
Daily dose = 10 mg; $t_{1/2} = 7$ h; $C_{\max} = 52$ ng/mL; $t_{\max} = 2$ h
52 ng/mL after 2 h
26 ng/mL after 9 h
13 ng/mL after 16 h
6.5 ng/mL after 23 h
6.0 ng/mL after 24 h (= C_{\min})
6.0 ng/mL - 20% = 4.8 ng/mL (= $C_{\min-20\%}$)
