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THE CLINICAL APPLICABILITY OF MONITORING ANTIHYPERTENSIVE DRUG LEVELS IN BLOOD

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BACKGROUND

- Suboptimal (pharmacological) treatment of hypertension leads to higher risks of cardiovascular and kidney disease.
- Non-adherence to antihypertensive drugs (AHDs) is one of the main causes of not reaching blood pressure targets.
- Therapeutic drug monitoring (TDM) by means of a venipuncture is the most reliable method to assess non-adherence, but can also provide quantitative drug concentrations.
- A dried blood spot (DBS) method is a convenient and patient friendly method that can be performed in the doctors office.

AIMS

1. **Evaluation of the clinical applicability of measuring drug concentrations of eight antihypertensive drugs and 4 active metabolites, using dried blood spot (DBS) and venipuncture.**

2. **Evaluation of the interpatient variability in drug concentrations and determination of variables that are of influence on the drug concentration.**

METHODS

All samples are measured with UPLC-MS/MS. The following drugs and [metabolites] were analysed simultaneously:
Amlodipine, Enalapril [Enalaprilate], Hydrochlorothiazide, Losartan [Losartan-carboxylic acid (ca)], Nifedipine, Perindopril [Perindoprilate], Spironolactone [Canrenone] and Valsartan.
Patients were eligible if their blood pressure was <135/85 mmHg, assuming adherence to antihypertensive drugs. All patients had to use ≥2 drugs that are mentioned above.

- Drug levels from DSB (whole blood) and plasma (venipuncture is considered the gold standard) were compared to determine false positive and negative values.
- Only plasma concentrations were used to determine inter-patient variability. The lowest and highest concentrations from each drug in one dose was compared around the supposed maximum drug concentration (T_{max}).
- Generalized Estimating Equation (GEE), a generalized linear model, was used to examine the influence of sex, time between intake and sampling, dose, weight and age of the patient on the drug concentration.

RESULTS

In total 135 patients were included, 40.8% female, from which both DBS and plasma were retrieved.

Figure 1 Plasma concentration time curve [canrenone] (N = 40)

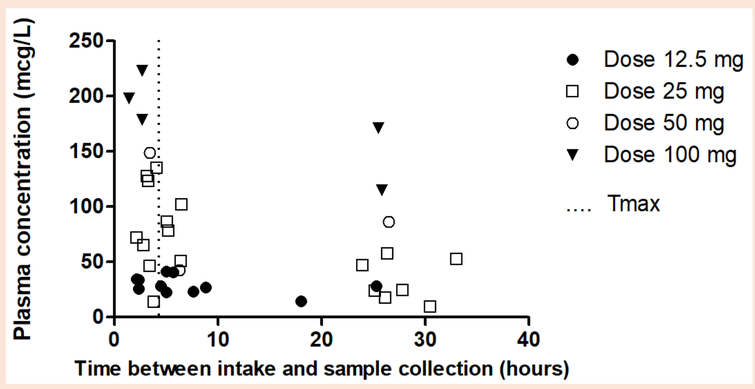


Table 1 False negative values per drug for DBS and plasma in percentage of total measured samples per drug

Drug [metabolite]	Samples	False negative DBS	False negative plasma
	N	%	%
Amlodipine	66	1.5	4.5
[Enalaprilate]	38	3.0	0
Hydrochlorothiazide	85	9.5	5.9
[Losartan-ca]	42	0	0
Nifedipine	40	2.5	0
[Perindoprilate]	41	9.6	2.4
[Canrenone]	43	0	2.3
Valsartan	42	0	0

Table 2 Fold-change in plasma concentrations at T_{max} of antihypertensive drugs with a same dosage

Drug [metabolite]	Dose (mg)	Fold-change plasma concentration at supposed T_{max}* (mcg/L)			Supposed T_{max} (hours)
		Lowest concentration	highest concentration	Fold - change	
Amlodipine	10	11.0	46.10	4.19	6-12
[Enalaprilate]	20	51.4	139.6	2.71	4
Hydrochlorothiazide	12.5	39.6	105.3	2.66	4
[Losartan-ca]	100	18.1	637.0	35.2	4
Nifedipine	60	20.9	89.80	4.30	1.6-4.2
[Perindoprilate]	8	4.70	45.30	9.61	3-4
[Canrenone]	25	42.0	98.00	2.30	4.3
Valsartan	320	1310.9	6876.4	5.25	2-4

* Fold-change plasma was calculated with data from approximately 0.5 hours around the supposed T_{max} if no range was supposed.

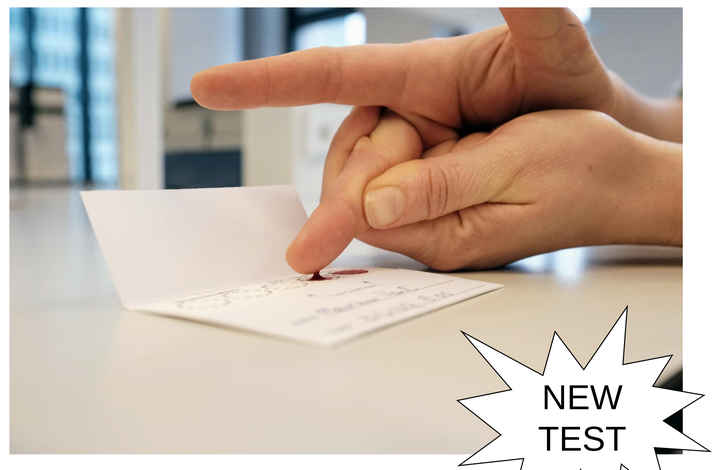
Table 3 Average difference in plasma concentrations in relation to sex, time after intake, dosage, body weight and age measured with GEE

Drug [metabolite] (mcg/L)	Female (%)	Male vs female	Time (h)	Dose (mg)	Weight (kg)	Age (year)
Amlodipine	30.5	-4.8	**-0.21***	**1.50‡**	-0.16	0.12
[Enalaprilate]	39.4	-12	**-3.1†**	-1.90	-0.93	-0.03
Hydrochlorothiazide	43.5	-31	-3.0	0.74	-0.75	1.10
[Losartan-ca]	47.6	17	**-9.4‡**	5.80†	**-6.28†**	12.0
Nifedipine	51.4	-4.5	-1.0	0.12	0.20	0.73
[Perindoprilate]	27.5	1.9	**-0.50‡**	0.55	-0.03	**0.26***
[Canrenone]	42.3	**30***	**-2.1‡**	**0.17***	-0.32	**-3.33†**
Valsartan	48.8	408	**-109‡**	**8.30†**	24.0	12.0

Results are based on multivariable linear regression, including the listed covariates.*P=0.01–0.05, † P<0.001, ‡ P=0.001–0.01.

CONCLUSIONS

- **DBS is a reliable and convenient method** to assess non-adherence to antihypertensive drugs
- **One size does NOT fit all:**
  high interpatient variability in plasma concentrations of all 8 measured antihypertensive drugs
- **0 mcg/L = non-adherence:**
  only undetectable antihypertensive drug levels can be used to confirm non-adherence



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