

Medication adherence during work-up for Conn syndrome

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Objective: Intake of incompatible drugs may significantly and unexpectedly bias biochemical results during laboratory evaluations for secondary hypertension. However, the role and rates of medication adherence and unwanted drug use during this process are still unclear. We performed plasma drug monitoring by LC-MS/MS to analyze medication adherence during our diagnostic 2-step protocol.

Setting, Study population

- Academic outpatient department, hypertension clinic
- All new referrals ≥ 18 years, recruitment period 12 months
- Inclusion: BP $> 140/90$ on 1st visit, ≥ 2 antihypertensives for ≥ 3 months (difficult-to-treat hypertension)
- Exclusion: COPD $\geq 3^\circ$, Heart failure NYHA IV, CKD $\geq 4^\circ$, mandatory drugs

Diagnostic 2-step protocol

- 1st visit: history, routine clinical and laboratory exams, stop all incompatible drugs (ACE-Inhib, ARBs, diuretics, b-blockers, central sympatholytics), Ca-A. allowed
- 2nd visit: ≈ 14 days later; standardized lab conditions, aldosterone/renin ratio, other tests, blood samplings 1h supine 8:30-9:30 am

Plasma drug monitoring by LC-MS/MS

- blood samples on 1st and 2nd lab visit
- 10 of 18 prescribed antihypertensives were checked in all samples
- about 75% of all prescriptions checked (60/79 vs. 20/26)
- Measured concentrations indexed for expected C_{max}

Patient characteristics, n=24

Age (years)	54 \pm 13
Female (%)	42
Body weight (kg)	82 \pm 22
eGFR (ml/min/1.73 m ²)	81 \pm 24

Prescribed medication

	1 st visit	2 nd visit
Number of pills taken, any reason	5.2 \pm 3.6	3.8 \pm 3.1
Antihypertensive drugs per patient	3.2 \pm 1.1	1.1 \pm 0.7**
Number of pills per patient for hypertension	2.5 \pm 1.0	1.1 \pm 0.7**

** p<0.01 (Mann-Whitney)

Plasma screening results (n=24)

	1 st visit	2 nd visit
Nonadherence or unreported drug intake	33%	25%
Nonadherence alone	21%	0%
Unexpected drug intake	12%	25%
Incompatible drug intake, not reported	-	21%
Failure to stop incompatible drugs	-	13%

Qualitative plasma drug screening:

Non-congruent with prescriptions : **33.3%**

Nonadherence: **21%** (1 of 5 patients)

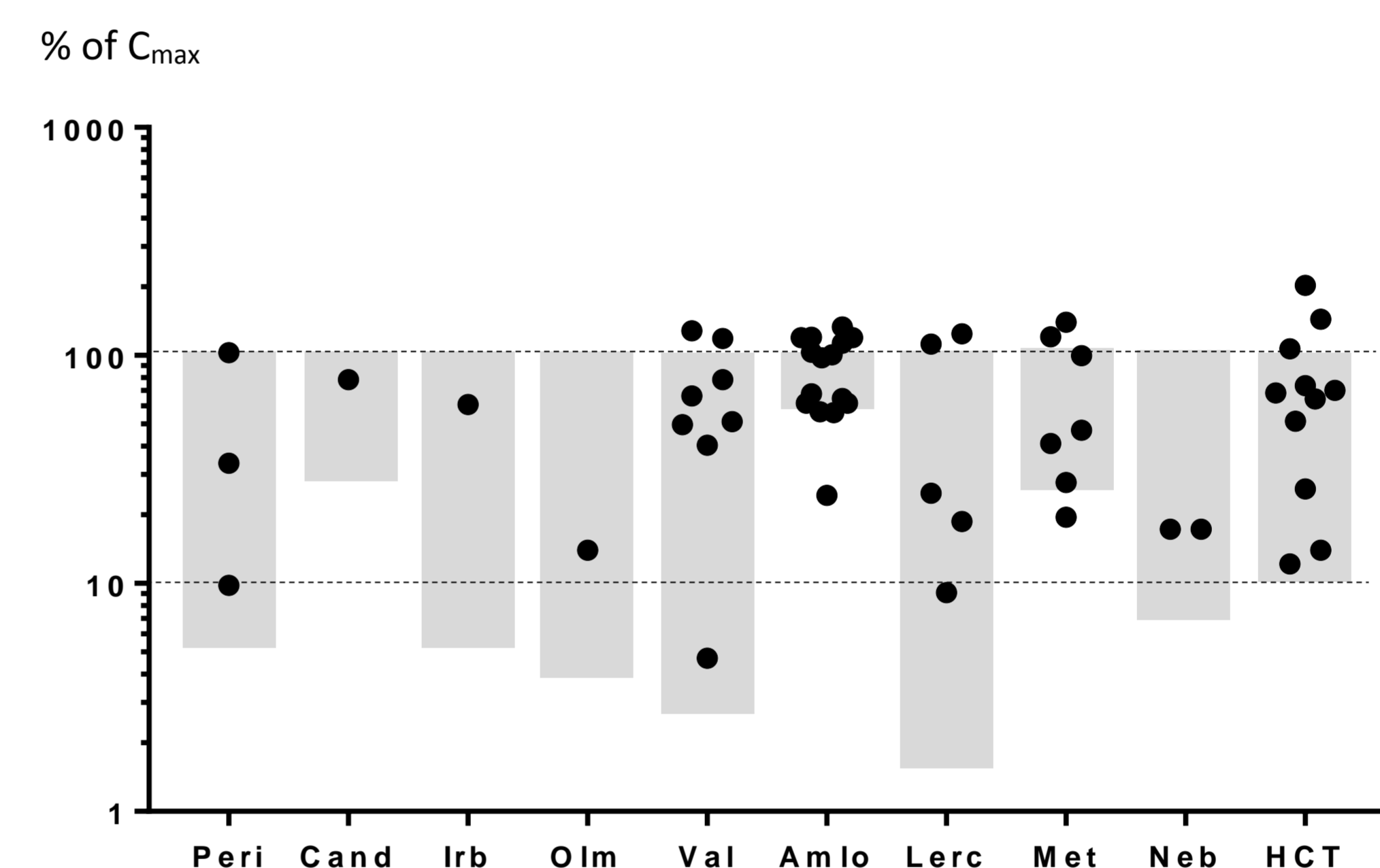
Unexpected drug use : **12 – 25%**

Incompatible drug use 2nd visit: **21%** (laboratory bias)

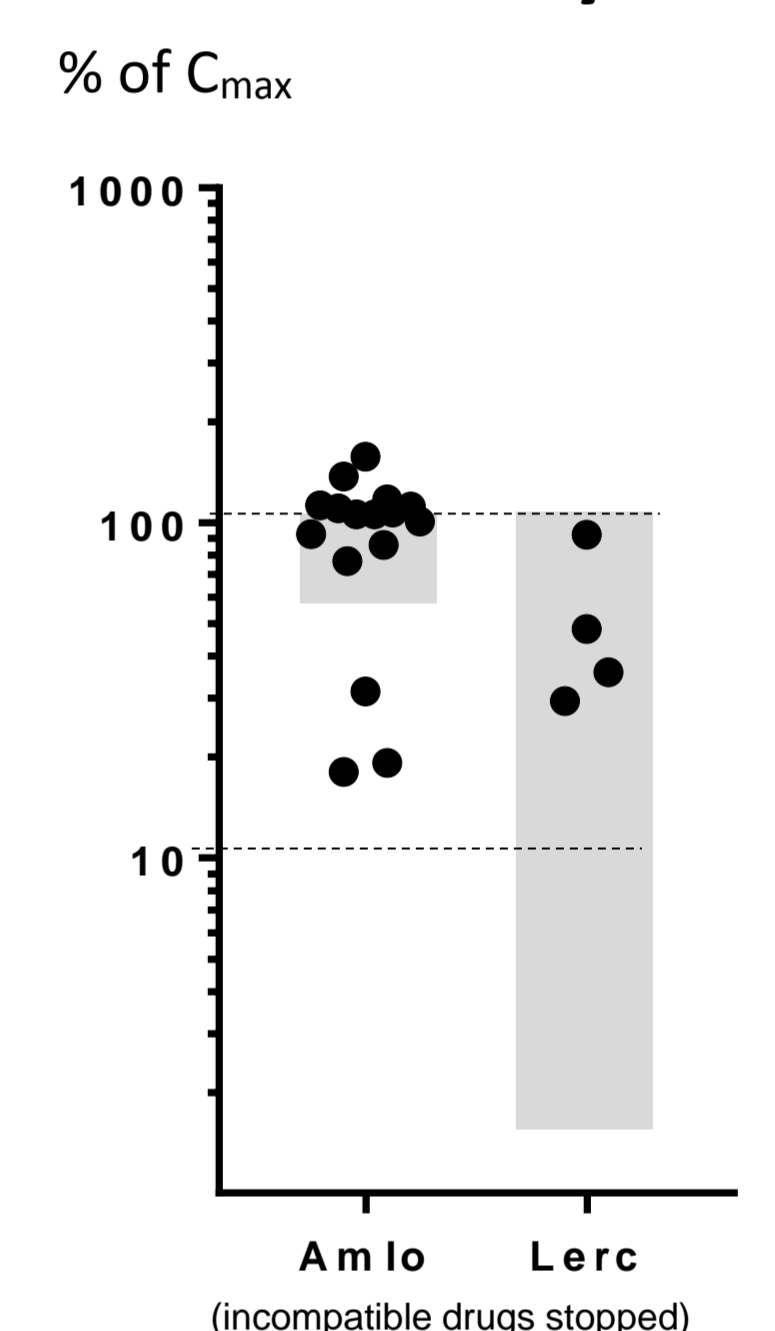
Plasma drug concentrations (LC-MS/MS)

prescribed and detected drugs, indexed for expected C_{max}
bars: maximum expected peak to trough concentr. range for lowest dose, once daily (QD)

1st admission visit



2nd laboratory visit



Plasma drug concentrations $\leq C_{min}$:

Up to 17% of patients additionally nonadherent = **previous day intake**

Screened drugs and plasma results

Drug	daily dose (mg/d)	1 st visit			2 nd visit		
		prescribed	assay positive, prescribed	assay positive, not prescribed	prescribed	assay positive, prescribed	assay positive, not prescribed
<i>Allowed on 2nd visit</i>							
Amlodipin	5 - 10	15	15		16	16	1
Lercanidipine	10 - 20	6	5	1	4	4	1
<i>Incompatible on 2nd visit</i>							
Candesartan	16 - 32	2	1		0		
Irbesartan	150	1	1		0		
Olmesartan	20	1	1		0		
Valsartan	160 - 320	8	8		0		
Perindopril ¹	2.5 - 10	3	3		0		2
Hydrochlorothiazide	6.25 - 50	12	11		0		
Metoprolol	25 - 100	9	7	1	0		2
Nebivolol	2.5 - 5.0	3	2	1	0		1
All drugs		60	54	3	20	20	7

¹ analysis of perindoprilat

³ LOQ's were 1.0 ng/ml for amlodipine, metoprolol, olmesartan, candesartan and hydrochlorothiazide; 0.25 ng/ml for lercanidipine, nebivolol; 0.5 ng/ml for perindoprilat; 50 ng/ml for Valsartan, Irbesartan

Conclusions:

- Unreported drug use is frequent during work-up of difficult-to-treat hypertension and may bias aldosterone/renin ratio determinations.
- Physicians should interpret biochemical results cautiously in view of possible medication bias and seek confirmation in unclear cases.