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Systematic Study on Time-Dependent Postmortem Redistribution of Antidepressants and Neuroleptics

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1. Introduction

Postmortem changes in the human body can influence drug concentrations and hence may significantly complicate the interpretation of postmortem forensic toxicological cases. Summarized under the term postmortem redistribution (PMR) are all artificially altered drug concentration changes after death (1). Particularly diffusion processes, degradation or drug-neo formation driven by microorganisms are thought to lead to such site- and time-dependent drug concentration changes. Based on their physicochemical properties, most anti-depressants and neuroleptics are thought to be susceptible to PMR (basic, generally lipophilic substances with large volume of distribution). Hence, time-dependent PMR of quetiapine, citalopram, mirtazapine, risperidone, 9-OH-risperidone, venlafaxine and O-desmethylvenlafaxine (ODMV) in blood and alternative matrices was investigated utilizing a computed tomography (CT)-guided biopsy tool.

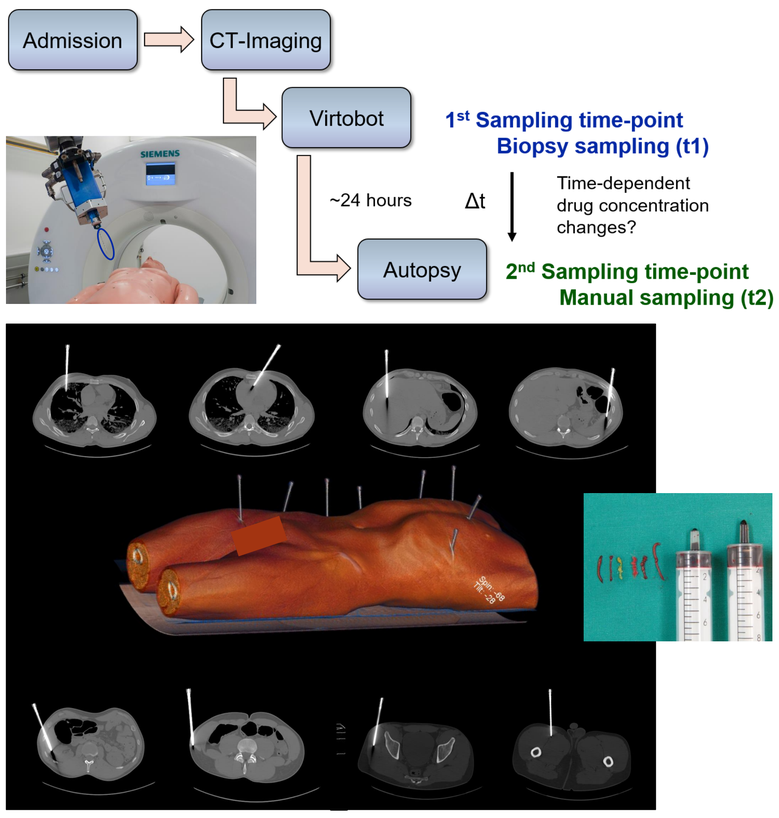

Fig.1: Postmortem sample collection workflow, visualizing the CT-guided «Virtobot» system (t1); biopsy needles (co-axial introducer needles) were placed into the the right lung, right heart ventricle (HB), the right lobe of the liver, the spleen, the right kidney, subcutaneous adipose tissue of the waist, muscle tissue of the right upper thigh and the right femoral vein (pB); samples were collected manually with a biopsy tool; approx. 24 h after the Virtobot sampling procedure (mean 23 ± 9.3 h; bodies stored at 7 °C between sampling points), tissue and body fluid samples from the same body regions were collected manually during the medico-legal autopsy (t2) (2).

2. Analytical Methods

Organ and tissue samples were first homogenized using a Fast Prep®-24 Instrument (MP Biomedicals, Illkirch, France). Sample extraction was performed using a two-step liquid-liquid extraction (LLE) with butyl acetate/ethyl acetate (1:1, v/v) at pH 7.4 and pH 13.5, respectively. After combination of the extracts, the samples were evaporated to dryness and reconstituted in 60 µL mobile phase (eluent A/B 90:10 (v/v); eluent A: 10 mM ammonium formate buffer in water containing 0.1% (v/v) formic acid; eluent B: acetonitrile containing 0.1% (v/v) formic acid). Targeted quantitative analysis was carried out on a Thermo Fischer Ultimate 3000 UHPLC system (Thermo Fischer, San Jose, California, USA) coupled to a Sciex 5500 QTrap linear ion trap quadrupole mass spectrometer (Sciex, Darmstadt, Germany) (3).

3. Results and Discussion

- **Quetiapine** cases demonstrated a correlating behavior with the postmortem interval (PMI) in pB, indicating multiple stages of time-dependent PMR.
- **Citalopram** cases showed a trend for time-dependent concentration decreases in pB, while for **mirtazapine** a trend for concentration increases in pB over time was observed; these results are in line with previous time-dependent investigations (4).
- **Risperidone and 9-OH-risperidone** pB concentrations both increased and decreased over time; concentrations in all central sites (e.g. HB, liver and lung) decreased between t1 and t2, likely due to bacterial degradation.
- Only minimal concentration changes in pB were observed for **venlafaxine and ODMV**, which contradicts previous studies, but could be caused by inter-individual variability within the limited sample set (4, 5).

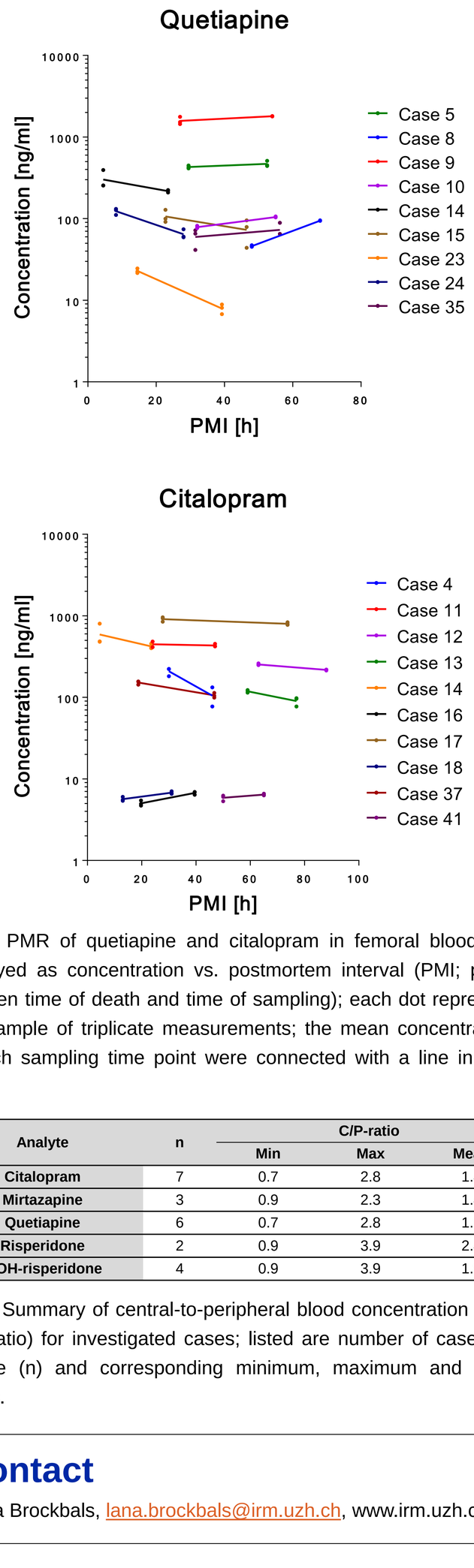

Fig.2: PMR of quetiapine and citalopram in femoral blood (pB) displayed as concentration vs. postmortem interval (PMI; period between time of death and time of sampling); each dot represents one sample of triplicate measurements; the mean concentrations at each sampling time point were connected with a line in each case.

Analyte	n	C/P-ratio		
		Min	Max	Mean
Citalopram	7	0.7	2.8	1.4
Mirtazapine	3	0.9	2.3	1.4
Quetiapine	6	0.7	2.8	1.8
Risperidone	2	0.9	3.9	2.4
9-OH-risperidone	4	0.9	3.9	1.8

Fig.3: Summary of central-to-peripheral blood concentration ratios (C/P-ratio) for investigated cases; listed are number of cases per analyte (n) and corresponding minimum, maximum and mean values.

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Conclusion

- Significant time-dependent concentration changes indicate the occurrence of PMR for most investigated analytes.
- No case interpretation had to be adjusted, which would suggest that PMR changes of antidepressants and neuroleptics do not seem to be relevant for forensic case interpretation.
- Proposed redistribution mechanisms: passive diffusion processes along the muscle-to-pB, liver-to-HB and lung-to-HB concentration gradients (citalopram, mirtazapine, quetiapine, risperidone and 9-OH-risperidone) and bacterial degradation (risperidone and 9-OH-risperidone).
- Limitations: time between death and t1 could not be controlled and bodies were stored in temperature-controlled environment between t1 and t2.

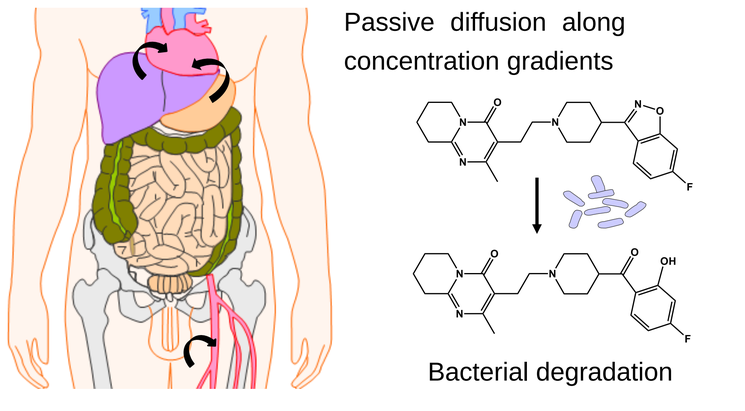

Fig.4: Visualization of potential redistribution mechanisms; risperidone is converted to 2-hydroxybenzoyl-risperidone.

Analyte	Matrix	n	Percentage concentration differences			
			Min [%]	Max [%]	Mean [%]	Median [%]
Citalopram	pB	10	-50	+34	-10	-13
	HB	7	-39	+39	+14	+25
	muscle	8	-32	+84	+3	-10
	liver	8	-25	+16	0	+1
	lung	8	-46	+60	-9	-19
Mirtazapine	pB	7	-15	+41	+12	+5
	HB	3	0	+142	+57	+29
	muscle	5	-6	+56	+18	+19
	liver	5	-18	+17	-4	-11
	lung	5	-42	+77	-7	-21
Quetiapine	pB	9	-65	+105	+3	+9
	HB	6	-55	+80	+12	+11
	muscle	8	-25	+83	+23	+16
	liver	10	-32	+29	+2	+2
	lung	10	-32	+69	+3	-6
Risperidone	pB	5	-74	+71	+7	+30
	HB	2	-72	-14	-43	-43
	muscle	3	-44	+19	-17	-27
	liver	3	-39	+7	-16	-16
	lung	3	-66	+2	-22	-3
	spleen	3	-21	+6	-7	-6
9-OH-risperidone	pB	8	-74	+75	+8	+5
	HB	4	-51	+18	-19	-21
	muscle	5	-35	+8	-16	-23
	liver	5	-37	+10	-12	-7
	lung	5	-67	+13	-24	-12
	spleen	5	-55	0	-26	-16
Venlafaxine	pB	7	-46	+28	-1	+2
ODMV	pB	5	-11	+17	+3	+4

Fig.5: Summary of time-dependent percentage concentration differences between t1 and t2 across analyzed cases; listed are number of cases per analyte (n), investigated matrix (pB refers to femoral blood and HB refers to heart blood) and corresponding minimum, maximum, mean and median values in percent; ODMV refers to O-desmethylvenlafaxine.

References

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