Oral fluid/serum ratio of Pregabalin and ten other psychoactive therapeutic drugs

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Introduction

Abuse of Pregabalin (P) and other psychoactive therapeutic drugs (PTD) occurs among opiates addicts and other patient groups. This has been supported by a communication about the dependence potential of P issued by the Drug Commission of the German Medical Association (2011) and a database query on P abuse and dependence in Germany (Gahr et al., 2013). Little is known about the positive prevalence rate of P and other PTD among addicts. We therefore established P in our routine UPLC-MS/MS multi-target screening method for oral fluid (OF). Knowledge about the OF/serum ratio of PTD is rare but a prerequisite for abuse screening in OF. Hence, an initial study was conducted to determine the ratio of P and these ten additional PTD from patients in steady-state: Aripiprazole, Citalopram, Duloxetine, Escitalopram, Mirtazapine, Pipamperone, Promethazine, Quetiapine, Sertraline and Venlafaxine.

Methods

Patient samples: Paired serum (SE) and OF samples (n = 102) were taken from patients, hospitalized for different psychiatric disorders, when in steady-state for the corresponding PTD prior to their next therapeutic dose (see Tab. 3). The study was approved by the ethics committee at the University of Mainz. P positive prevalence rate in OF was calculated retrospectively from our routing drug screening results of a three month period (2050 patients, 5355 samples ; see Tab. 2). **Sample collection:** SE was prepared from blood collected by venous puncture. OF samples were collected using the liquid based Greiner-Bio-One (GBO, Austria) SCS pH 4.2 device according to the manufacturer (see pictures below). % OF concentration of the OF/SES mixture was quantified on an Olympus AU680 using the GBO saliva quantification kit. **Chromatographic methods:** Sample preparation and chromatographic separation of the PTD in SE and OF was performed using the commercial MassTox® TDM Series A Kits (Chromsystems, Germany ; LoQs: 0.5 to 5.0 ng/mL) on a Waters Acquity UPLC system connected to a Xevo TQ-MS detector. Routine P screening and quantification in OF was performed with our routine multi-target-screening method for OF (n = 56 analytes) on a Waters Acquity/Xevo TQ-S UPLC-MS/MS applying a cutoff at 1.0 ng/mL neat OF. The corresponding deuterated standard P-d6 was fortified at a concentration of 0.5 ng/mL OF/SES.

Conclusion

-- The P OF/SE ratio was low (mean 0.1). However, therapeutic and abused doses are high, thus abuse detection in OF is possible.

-- P abuse at the moment is much more prevalent in south Germany (Munich area, Stuttgart area) than in the north-eastern part (Berlin area, Leipzig area).

-- All other investigated PTD with the exception of Aripiprazol revealed promising OF/SE ratios. Taking into consideration the therapeutic dosing and a cutoff at 1 ng/mL, abuse and compliance testing in OF seems possible.

Results

Tab. 1 Oral fluid/serum concentration ratios of investigated drugs

drug	n	ratio [OF/SE] mean	pKa	PPB [%] *	ratio [OF/SE] median	ratio [OF/SE] range	ratio [OF/SE] CV [%]	OF vs. serum intercept	OF vs. serum slope	OF vs. serum R^2
Aripiprazole	7	0.10	7.6	99	0.09	0.05-0.17	50	11.26	0.02	0.21
Citalopram	9	5.17	9.5	~ 80	4.46	2.63-9.61	52	-45.26	6.16	0.49
N-Desmethylcitalopram	9	1.13	n/a	n/a	0.74	0.40-2.96	71	9.93	0.72	0.15
Duloxetine	10	0.61	9.3	90	0.60	0.34-0.94	33	12.91	0.49	0.51
Escitalopram	24	6.10	9.5	~ 80	5.64	1.59-13.44	59	7.21	6.06	0.46
L-Desmethylcitalopram	22	1.42	n/a	n/a	1.03	0.23-5.00	85	17.43	3.24	0.57
Mirtazapine	14	4.52	7.7	85	4.23	1.36-7.97	35	10.17	4.12	0.69
Pipamperone	9	7.12	8.2	n/a	5.18	1.41-15.71	70	119.67	3.94	0.31
Pregabalin	8	0.10	4.2/10.6	0	0.10	0.01-0.19	50	56.85	0.07	0.24
Promethazine	6	3.26	9.1	80	3.07	1.83-4.55	31	0.25	3.29	0.96
Quetiapine	14	0.94	3.3/6.8	83	0.95	0.45-1.85	35	-9.41	0.99	0.87
Sertraline	4	1.07	9.2	98	0.93	0.62-1.81	49	4.21	0.96	0.23
N-Desmethylsertraline	4	1.07	n/a	n/a	0.60	0.46-1.39	57	19.48	19.48	0.34
Venlafaxine	39	8.47	9.4	27	7.72	2.04-16.65	47	-194.35	10.41	0.79
N-Desmethylvenlafaxine	39	2.61	n/a	30	2.46	0.58-6.23	58	69.28	2.28	0.39

* red and bold: Fig. 1 - Fig. 5

* plasma proteine binding according to literature

Fig. 2 Escitalopram: oral fluid vs. serum conc.

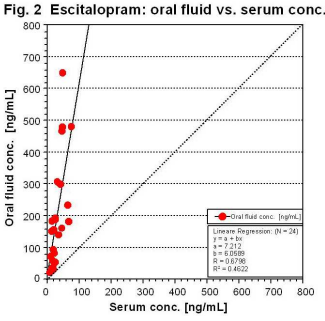


Fig. 3 Venlafaxine: oral fluid vs. serum conc.

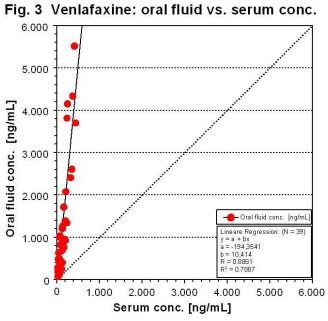


Fig. 4 Mirtazapine: oral fluid vs. serum conc.

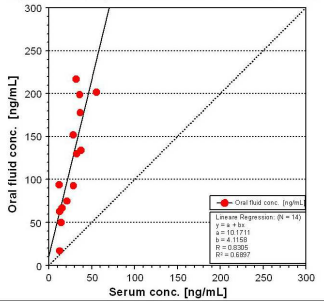
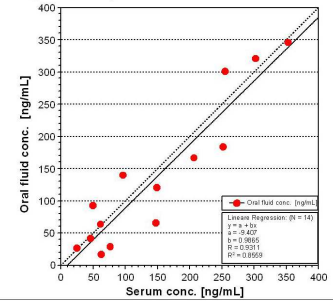
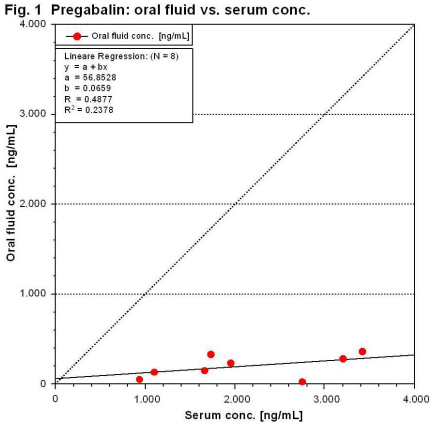


Fig. 5 Quetiapine: oral fluid vs. serum conc.



Pregabalin was integrated in our routine OF drug screening method. During a three month period 5355 spls. from 2050 pats. (1455 m, 595 f) were analysed: 2.5% of the spls. and 4.5% of the pats. were positive for Pregabalin. However, there was a clear **"north-south difference".**

Fig. 1 Pregabalin: oral fluid vs. serum conc.



Tab. 2 Pregabalin: north-south difference in prevalence

region	n total	[%]	n positive	[%]	prevalence rate [%]
samples from South Germany	410	7.7	77	56.6	18.8
samples from North Germany	4945	92.3	59	43.4	1.2
total	5355		136		2.5

Tab. 3 Study conditions / patients data

drug	n male	n female	n patients	age	daily dose [mg] range	no. of pats. without any co-medication
Aripiprazole	3	4	7	26-65	5 - 30	-
Citalopram	3	6	9	31-64	20 - 60	2
Duloxetine	1	9	10	43-81	30 - 120	-
Escitalopram	9	15	24	21-77	10 - 40	4
Mirtazapine	7	7	13	44-76	7.5 - 45	1
Pipamperone	3	6	9	22-77	20 - 100	-
Pregabalin	5	3	8	27-58	50 - 400	-
Promethazine	3	3	6	47-74	unknown	-
Quetiapine	4	10	13	22-81	50 - 700	-
Sertraline	1	3	4	22-73	100 - 150	-
Venlafaxine	17	22	37	22-76	75 - 375	5

Paired SE and OF samples (n=102) were taken from 98 pats. 55 individuals were treated with one (12 without any co-medication), 31 with two and 12 with three of the studied drugs. Samples with values resulting from oral contamination (n = 5) or sampels. from patients obviously not in steady-state (n = 5) were excluded.

Saliva Collection System (SCS) pH 4.2

Saliva collection

(1) rinse oral cavity with Saliva Extraction Solution (SES) for minimum 2 minutes
(2) spit OF/SES into beaker
(3) transfer OF/SES into evacuated tubes containing bactericides and send to lab
(4) after centrifugation Amylase and OF concentration are determined on an Olympus AU680