**Lower sertraline plasma concentration in patients co-medicated with clozapine – Implications for pharmacological augmentation strategies in schizophrenia**

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**What is already known about this subject**

* Augmentation of clozapine with SSRIs such as sertraline may be beneficial for negative and depressive symptomatology in patients with schizophrenia
* No available data provide knowledge on the impact of clozapine on plasma concentrations of sertraline

**What this study adds**

* Treatment with clozapine is associated with significantly lower plasma concentrations of sertraline.
* Clinicians should consider therapeutic drug monitoring for dose adjustment of sertraline when added to a clozapine treatment

**Abstract**

**Aim:** Augmentation of antipsychotic treatment with antidepressants represents a common and beneficial treatment strategy in patients suffering from schizophrenia. Combining clozapine and the selective serotonin reuptake inhibitor (SSRI) sertraline represents a clinically important strategy, but there is limited knowledge about mutual pharmacokinetic interactions. In the present study, we assessed the impact of clozapine on sertraline plasma concentrations.

**Methods:** Based on a therapeutic drug monitoring (TDM) database, sertraline plasma concentrations were compared between two groups: patients receiving a combined treatment with sertraline and clozapine (SERTCLZ; N=15) and a matched control group receiving sertraline but no clozapine (SERT; N=17). Group differences with respect to raw and dose-adjusted plasma concentrations were assessed using non-parametric tests.

**Results:** No significant differences were found between the groups regarding daily dosage of sertraline, age, weight, sex distribution, and caffeine or nicotine consumption (all p-values >0.05). Co-medication with clozapine was associated with 67% lower median sertraline plasma concentrations (16 vs. 48 ng/mL; p=0.022) and 28% lower median dose-adjusted plasma concentrations (C/D; 0.21 vs. 0.29 (ng/mL) / (mg/day); p=0.049) as compared to the control group.

**Conclusion:** When applying a combined treatment with clozapine and sertraline, clinicians should consider therapeutic drug monitoring to confirm therapeutically effective plasma concentrations of sertraline.

**Introduction**

Growing evidence emphasizes beneficial effects of well-chosen pharmacological augmentation strategies in the treatment of schizophrenia 1, 2. In particular, adding antidepressants to antipsychotic monotherapy may alleviate negative symptoms, reduce obsessive compulsive behavior and may improve depressive symptomatology 3. Notably, about one third of patients suffering from schizophrenia fulfill the criteria of a comorbid major depressive disorder 4-6, thus significantly exceeding the prevalence of the general population. Accordingly, the concomitant prescription of antidepressant and antipsychotic medication represents a common clinical practice 7. Among the different antipsychotic drugs, clozapine is the only antipsychotic with proven efficacy in treatment-resistant schizophrenia 8. The drug is characterized by a pleiotropic receptor profile exerting agonistic effects on the dopamine D1-, serotonin 5-HT1A-, muscarinic cholinergic M4- and NMDA-receptor and antagonistic effects on the dopamine D2- and D4-, serotonin 5-HT2A- and 5-HT2C-, adrenergic α1- and α2-, histaminergic H1-, muscarinic cholinergic M1-, M2- and M3- as well as the GABAA-receptor9. It is extensively metabolized via cytochrome P450 (CYP) isoenzymes mainly involving CYP1A2, 2C19, 2D6, and 3A4 10, 11 and plasma concentrations between 350–600 ng/mL are considered to be therapeutically effective 11. Selective serotonin reuptake inhibitors (SSRIs) are among the most widely prescribed antidepressant drugs 12. Based on meta-analytical evidence sertraline is among the most effective antidepressant agents, with a fair tolerability profile 13. Sertraline is generally considered to be devoid of clinically relevant CYP inducing or inhibiting properties although it exerts weak inhibitory effects on CYP2C19, 2C9, 3A4 and 2D6 14, 15.

Sertraline’s metabolism includes N-demethylation (catalyzed by CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), deamination (catalyzed by CYP2C19, CYP3A4, and monoamine oxidases A and B) as well as N-carbamoyl glucuronidation, mediated by UDP-Glucuronosyltransferase-2B7 16. Sertraline’s elimination half-life is between 22 and 36 hours 11 and plasma concentrations in a range between 10 and 150 ng/mL are considered as therapeutically effective 11.

Only few studies addressed pharmacokinetic or pharmacodynamical interactions between clozapine and sertraline 17, 18. Specifically, a tendency towards higher plasma concentrations of clozapine in patients co-medicated with sertraline compared to clozapine monotherapy has been described in a study controlling for smoking status 17. To the best of our knowledge, however, there has been no study addressing the effects of clozapine on sertraline plasma concentrations in patients treated with the combination of clozapine and sertraline. Therefore, we conducted a retrospective analysis of sertraline plasma concentrations from a therapeutic drug monitoring database comparing sertraline concentrations in patients with and without co-medication with clozapine.

**Methods**

KONBEST, a web-based laboratory information management system for therapeutic drug monitoring laboratories 19 served as our data source. The original dataset comprised 1,295 sertraline plasma concentrations from 874 patients. Data were collected between 2006 and 2015 as part of the clinical routine in different institutions of the AGATE (Arbeitsgemeinschaft Arzneimitteltherapie bei psychischen Erkrankungen). AGATE represents a collaboration for drug safety in the treatment of mental disorders (for details see: www.amuep-agate.de). Retrospective analysis of clinical data was in accordance with the local regulatory authority of the medical faculty of the RWTH Aachen University. In this naturalistic database, patients received treatment with sertraline for different reasons. Patients who received a concomitant pharmacological treatment with possible inhibitory or inducing properties for CYP2B6, CYP2C19, CYP3A4 or inhibitory properties for CYP2D6, according to the suggestions by the US Food and Drug Administration 11, 20, were excluded from the analysis. Among patients with more than one measurement of sertraline plasma concentration, we selected the most recent measurement 21. Hence, TDM data of 794 in- and outpatients with a broad spectrum of psychiatric diseases were eligible for analysis. Based on this sample, we considered two groups: a group of patients receiving sertraline with co-medication with clozapine (SERTCLZ, N=15) and a control group receiving sertraline, but no clozapine (SERT, n=17). The control group was extracted out of the remaining 779 patients who did not receive clozapine, and we matched the 17 best fitting patients with respect to age and sex. Demographic and clinical characteristics of the sample are provided in Table 1.

*Quantification of sertraline*

Blood samples were drawn just before drug administration (i.e. trough levels) at steady-state conditions (> 5 elimination half-lives under the same drug dose). All sertraline concentrations were determined in the same laboratory by high pressure liquid chromatography with ultraviolet detection (HPLC/UV) 22; unfortunately, no concentrations of the metabolite desmethylsertraline were available. The method applied here was validated according to DIN 32645 (Deutsche Industrie Norm 32645, described in the guidelines of the GTFCh (Society of Toxicology and Forensic Chemistry) in consideration of ISO 5725 (International Organization for Standardization) 23, FDA (US Food and Drug Administration) guidance (US Food and Drug Administration, 2018) 24, and ICH (International Conference on Harmonization) requirements 25. The laboratory regularly runs internal quality controls and participates in external quality assessment schemes by INSTAND (Düsseldorf, Germany, www.instandev.de).

Inaccuracy, inter- and intraday inaccuracy were evaluated at sertraline concentrations of 300, 100 and 5 ng / mL respectively.

* Inaccuracy: bias values were – 2.14 %, 2.80 % and 8.60 %
* Interday imprecision: coefficients of variation (CV) were 3.8 %, 8.9 % and 13.9 %
* Intraday imprecision: CVs were 0.8 %, 7.0 % and 10.4 %.

Lower limit of detection (LOD) and limit of quantification (LOQ) were 3.6 and 7.2 ng/mL, respectively.

*Statistical analysis*

Statistical analysis was carried out using MATLAB 2015a (The MathWorks, Inc., Natick, USA). Sertraline plasma concentrations were compared between the two groups SERTCLZ (N=15), and SERT (N=17). Dose-adjusted drug concentrations (ratio of the drug concentration C and the daily dose D, C/D, in [(ng/mL)/(mg/day)] were also calculated. Due to non-normal distributions of the sertraline concentrations, Mann-Whitney *U* test was chosen as a non-parametric test to compare the sertraline plasma concentrations between the two study groups.

**Results**

The demographic data of the study groups are displayed in table 1. No significant differences were found between the groups regarding daily dosage of sertraline, age, weight, sex distribution, and caffeine or nicotine consumption (all p-values >0.05). Median daily dose of clozapine in the SERTCLZ – group was 300 mg (interquartile range [Q1-Q3] = 150-400 mg).

[insert Table 1 about here]

Plasma concentrations of sertraline were lower in the group co-medicated with clozapine compared to the control group (p=0.022, Mann-Whitney *U* test, for detailed statistics see table 2); accordingly dose-adjusted drug concentrations were lower in the group co-medicated with clozapine compared to the control group (p=0.049, Mann-Whitney *U* test). Specifically, when compared to the control group, patients under a co-medication with clozapine exhibited 67% lower median plasma concentrations and 28% lower median dose-adjusted plasma concentrations of sertraline. Moreover, 3 of the 15 patients in the SERTCLZ group exhibited plasma concentrations below the therapeutic reference range (TRR) of sertraline (10–150 ng/ mL), whereas none of the patients in the SERT group exhibited sub-therapeutic concentrations. For a formal comparison of the proportions of patients above and below the lower limit of the TRR between the two groups, we also conducted a χ2-test that, however, could only confirm a trend-level difference in this regard (χ2(1) = 3.75; p=0.053).

[insert Table 2 about here]

[insert Figure 1 about here]

[insert Figure 2 about here]

**Discussion**

The augmentation of an antipsychotic treatment by adding an antidepressant drug represents a common and potentially beneficial strategy for targeting negative and depressive symptomatology in patients suffering from schizophrenia [7]26. The combined treatment with clozapine and sertraline is a clinically particularly meaningful combination due to clozapine’s superior potency with respect to treatment resistant schizophrenia and sertraline’s favorable efficacy and safety profile among different antidepressant drugs. While previous studies focused on the effect of sertraline on plasma concentrations of clozapine, the present study shows - to our knowledge - for the first time that a co-treatment with clozapine and sertraline is associated with significantly lower plasma concentrations of sertraline. Subsequent studies are warranted to fully unravel the mechanism of this finding. Indeed, in a recently published in vitro study using human hepatocytes, Danek et al. provided first preliminary evidence for a CYP3A4 inducing effect of clozapine 27. However, the effect was only significant for clozapine concentrations above the therapeutic reference range. An CYP3A4 inducing effect was further supported by Srisuma and coworkers28. The authors observed elevated plasma concentrations of sertraline associated with a serotonin syndrome three days after abrupt discontinuation of clozapine. Elevated drug concentrations may be explained by the end of the inducing effect of clozapine. Another potential mechanism beyond the CYP system might be clozapine’s inhibitory effect on gastrointestinal motility which is attributed to its antagonistic properties at muscarinic cholinergic, serotonergic and histaminergic receptors 29. Clozapine-induced gastrointestinal hypomotility typically manifests as constipation, but can also reach life-threatening stages 29-31. Importantly, decreasing the rate of gastric emptying and gastrointestinal motility generally leads to a reduced absorption of orally administered drugs 32. Consequently, the here reported lower sertraline plasma concentrations in patients under the concomitant therapy with clozapine may be related to a lower resorption of sertraline due to gastrointestinal hypomotility.

The present finding may raise the question whether other antidepressant drugs should be preferred over sertraline when considering an augmentation strategy to an antipsychotic treatment with clozapine. In general, SSRIs represent first choice agents due to their favorable properties regarding efficacy and toxicity. Moreover, they exhibit superior efficacy for the treatment of obsessive compulsive symptoms which are frequently observed in patients with schizophrenia, particularly patients under a treatment with clozapine 33, 34. Among the different SSRIs, fluoxetine and paroxetine may increase clozapine levels due to their CYP2D6 inhibiting properties 18, 35. Fluvoxamine is a potent CYP1A2 inhibitor and may be used to achieve therapeutically effective plasma concentrations in smokers 36. For citalopram and escitalopram, the cumulative effect on QTc prolongation should be taken into consideration 37-39. Therefore, sertraline may still be a favorable treatment option for the combination with clozapine, but clinicians may consider the use of therapeutic drug monitoring to confirm the achievement of therapeutically effective plasma concentrations as suggested by the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology 11.

**Limitations**

As we retrospectively conducted this analysis, patient information is likely less reliable than in prospective studies. A major limitation of the present study is the limited number of patients. Therefore, the quantitative estimates of clozapine’s impact on sertraline plasma concentrations have to be considered as rather uncertain. As a further limitation, plasma concentrations of desmethylsertraline, the main metabolite of sertraline, were not available. Moreover, many clinical parameters such as the duration of illness, the clinical phenotype, adverse effects, comorbidities, renal function parameters as well as the duration of prior treatment with sertraline and the co-medication were not available.

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Author contributions:

Participated in research design: AJG, GS, MP, CH, EH

Performed data analysis: AJG, MP

Wrote or contributed to the writing of the manuscript: AJG, GS, KE, EH, CH, MP

**Conflicts of interest statement**

Ekkehard Haen received speaker’s or consultancy fees from the following pharmaceutical companies: Servier, Novartis, and Janssen-Cilag. He is managing director of AGATE, a non-profit working group to improve drug safety and efficacy in the treatment of psychiatric diseases. He is editor of psiac, an internet based drug–drug interaction program for psychopharmacotherapy (www.psiac.de). He reports no conﬂict of interest with this publication. Christoph Hiemke has received speaker’s fees from Otsuka. He is editor of PSIAC, an internet based drug–drug interaction program for psychopharmacotherapy (www.psiac.de). He reports no conﬂict of interest with this publication. Michael Paulzen has received speaker’s fees from the following pharmaceutical companies: Neuraxpharm, Lundbeck, Janssen, Otsuka. He is editor of psiac, an internet based drug–drug interaction program for psychopharmacotherapy (www.psiac.de). He reports no conﬂict of interest with this publication. Georgios Schoretsanitis has served as consultant for HLS Therapeutics. All other authors report no conflicts of interests.

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**Data availability statement**

Data are stored at RWTH Aachen University hospital. The data are not publicly available due to privacy and ethical restrictions.

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**Figure Legends**

Figure 1: Comparison of sertraline plasma concentrations (ng/mL). Note the significantly lower value in the SERTCLZ-group, compared to the control group.

Figure 2: Dose adjusted sertraline plasma concentration (C/D) in [(ng/mL)/(mg/day)]. Note the significantly lower C/D value in the SERTCLZ-group, compared to the control group.