ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Cigarette smoking and heavy coffee drinking affect therapeutic response to olanzapine

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SUMMARY

Introduction/Objective Considering relatively complex pharmacokinetic profile of olanzapine, it is expected that certain medications and some compounds, found in food and drink, can induce or inhibit its metabolism.

The aim of our study was to investigate the influence of cigarette smoking and heavy coffee consumption on the clinical response to olanzapine.

Methods The phase IV, open-labeled, four-week-long prospective clinical trial included 108 adult patients diagnosed with schizophrenia. According to cigarette smoking (n = 52) and coffee drinking (n = 55), four subgroups were defined: non-smokers, non-heavy coffee consumers (group 1), non-smokers, heavy coffee consumers (group 2), smokers, non-heavy coffee consumers (group 3) and smokers and heavy coffee consumers (group 4). Positive and Negative Syndrome Scale (PANSS) and Global Assessment of Functioning (GAF) scales were used for therapeutic response evaluation.

Results Baseline and final GAF scores were 33.3 ± 5.0 and 61.5 ± 9.6, respectively, and PANSS scores were 100.7 ± 3.9 and 85.5 ± 5.4, respectively. The changes of GAF and PANSS scores from the baseline to the study end were 115.1 ± 35.7 and -19.6 ± 3.1, respectively (group 1), 91.1 ± 30.8 and -15.3 ± 2.9, respectively (group 2), 76.1 ± 29.8 and -13.4 ± 4.4, respectively (group 3), and 64.7 ± 29.3 and -11.3 ± 3.22, respectively (group 4), making significant subgroup differences for both scale scores (p < 0.001). Cigarette smoking and heavy coffee drinking significantly and independently diminished improvement in both GAF and PANSS total score (p < 0.001). Changes of body mass index from the baseline significantly influenced the change of PANSS total score only (p = n.s.), in a negative direction (r = -0.454, p < 0.001).

Conclusion Smoking and heavy coffee drinking influenced effects of olanzapine in patients with schizophrenia treated in routine practice.

Keywords: schizophrenia; antipsychotic agents; coffee; tobacco use

INTRODUCTION

The treatment of patients with psychotic disorders changed in recent decades, mainly due to the emergence of a new group of drugs called atypical, newer, or second-generation antipsychotics. They have fewer side effects, better compliance and, in some domains, improved efficacy in comparison to conventional antipsychotic drugs [1]. Olanzapine, an atypical antipsychotic of thienobenzodiazepine structure, has a broad pharmacological profile and it acts on dopamine ($D_1/D_2/D_3/D_4$), serotonin ($5\text{-}HT_{2A}/_{2C}$), muscarinic (M_1), histamine (H_1), and the adrenergic (α_1) receptors [2]. In clinical trials, in patients suffering from schizophrenia, or schizophrenia spectrum disorders, olanzapine has proved effective in treating both positive and negative symptoms, with a low incidence of extrapyramidal symptoms [3].

Antipsychotic efficacy of olanzapine is achieved in daily doses ranging 5–20 mg. Pharmacokinetics of olanzapine is characterized by a large volume of distribution, multiple biotransformation pathways, and a relatively long half-life, which require a slowly-titrating dosing regimen [4]. Several enzymes are involved in the metabolism of olanzapine, including cytochrome P450 1A2 (CYP1A2) and 2D6 (CYP2D6), flavin-containing monooxygenase 3 (FMO3), and UDP-glucuronosyltransferase 1A4 (UGT1A4) [5, 6, 7].

Considering such a relatively complex pharmacokinetic profile of olanzapine, it is expected that certain medications and some compounds, found in food and drink, can induce or inhibit its metabolism, changing the drug plasma levels. Therefore, drug interactions or genetic variability may require the use of doses that differ from those recommended for atypical antipsychotics [8]. For example, co-administration of olanzapine and the potent CYP1A2 inhibitors such as fluvoxamine or ciprofloxacin resulted in higher olanzapine serum concentrations [9]. In contrast, carbamazepine, a CYP1A2 inducer, causes the increase of clearance and volume of distribution of olanzapine [10]. Interethnic differences in the distribution of CYP1A2 alleles lie behind different catalytic activity of the cytochrome in different populations, for example in Orientals compared to Caucasians [11].

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Many patients with mental disorders are regular cigarette smokers, and their consumption of large amounts of caffeine-containing drinks is widespread. Earlier investigations showed that smoking can significantly decrease olanzapine levels, up to 50%, possibly due to effects of polycyclic aromatic hydrocarbons (PAHs) present in tobacco smoke [12]. PAHs are potent inducers of the hepatic cytochrome P-450 (CYP) isoenzymes 1A1, 1A2, and, possibly, 2E1 [13]. Therefore, starting or quitting cigarette smoking during ongoing therapy sometimes requires adjusting the dosing regimen and measuring olanzapine plasma levels [14]. Similarly, heavy coffee consumption increases CYP1A2 activity, most probably due to the effects of PAHs, which are formed during the roasting of coffee beans [15].

The separate effects of smoking and coffee drinking on the pharmacokinetics of psychotropic drugs, including olanzapine, are reasonably well documented in the literature. The relationships between pharmacokinetics and pharmacodynamics with the treatment response of antipsychotics, based on the standardized psychiatric rating scales, have been established [16]. However, little is known about the consequences of patients' life-style patterns on the antipsychotic therapeutic response.

Therefore, the aim of our study was to investigate the influence of cigarette smoking and heavy coffee consumption on clinical response to olanzapine in patients with schizophrenia. We hypothesize that these factors significantly change the therapeutic and adverse effects of the drug.

METHODS

This study was designed as a phase IV, open-labeled, prospective clinical trial in a cohort of patients with schizophrenia, which were treated with olanzapine. Recruitment of the subjects was conducted at the Psychiatric Clinic of the Kragujevac Clinical Centre, Serbia, from 2014 to 2016. One hundred and eight adult patients, meeting the DSM-V diagnostic criteria [17] for schizophrenia, and having either the first episode or the disease relapse, as assessed with BPRS (Brief Psychiatric Rating Scale) [18], were enrolled in the study. There exclusion criteria were as follows: younger than 18 years of age, pregnant or lactating women, psychotropic drugs other than benzodiazepine or hypnotic agents, the presence of disabling and medically uncontrolled somatic condition(s), known contraindications for olanzapine treatment, and subject's rejection of study participation. The participation was voluntary and subjects were included in the study after providing the written informed consent. The study was approved by the Ethic Committee of the Kragujevac Clinical Centre, Serbia, decision No 01/5273.

The study included three patient visits: at the baseline, and two and four weeks after the introduction of olanzapine treatment. Baseline visit encompassed the screening for the subject's eligibility for the study enrollment and collection of all necessary study data. Written information about the gender, age, psychiatric, and concomitant diseases and treatments, as well as the baseline cigarette smoking and

coffee consumption habit were obtained using a detailed questionnaire.

The oral olanzapine treatment was introduced according to the recommendation described in the British National Formulary, i.e. with the starting dose of 10 mg once daily. The clinical effectiveness of olanzapine treatment at the study visits was assessed using the Positive and Negative Symptoms Scale (PANSS) and the Global Assessment of Functioning (GAF) rating scale [19]. Olanzapine dose adjustments were performed according to the achieved clinical response and the drug tolerability.

During the study, the subjects were provided with a wide list of possible adverse effects that can occur during the olanzapine treatment, and the patients were encouraged to write down any noxious symptom if they experience it. The patients' diaries also included the information on the cigarette smoking habit and the daily intake of coffee. According to the data on coffee consumption and cigarette smoking, participants were divided into the following four groups: a) non-smokers, non-heavy coffee consumers (group 1), b) non-smokers, heavy coffee consumers (group 2), c) smokers, non-heavy coffee consumers (group 3), and d) smokers and heavy coffee consumers (group 4). Smoking on average two or more cigarettes per day defined a cigarette smoker, while regular daily intake of at least three cups of coffee defined a heavy coffee consumer.

Sample size was determined according to the expected differences in the primary variable, the percent change of PANSS total score from the baseline to the end of the study, between the users (group 4) and the non-users of cigarettes and at least three cups of coffee per day (group 1). We postulated the difference for independent samples of at least 10% with the standard deviation of 10%, at alpha error of 5% and the study power of 80%, for a two-sided t-test. The minimum number of 20 patients per subgroup was calculated [20]. The data analysis included descriptive statistics, hypothesis testing, and correlation, according to the type of the variable and data distribution, at the probability of null hypothesis of 5% or less, with a two-sided approach. The analysis of the primary variable was performed using a general linear model with the pattern of smoking and coffee consumption (study groups) and gender as fixed factors, and years of age, olanzapine dose, and the percent change of body mass index (BMI) from baseline as the covariates.

RESULTS

The main patients' demographic and clinical characteristics are presented in Table 1. In general, the number of male and female subjects was similar, with the average age within the fifth decade of life, and about one quarter being residents of a long-term psychiatric care facility. About one half of the study patients were smokers and heavy coffee drinkers, and the study groups comprised similar number of subjects.

Among the four study groups there were significantly different therapeutic responses as measured with GAF

Table 1. The patients' characteristics (n = 108)

Variable	Value
Gender (male/female)	53 (44.1) / 55 (50.9)
Age (years)	46.0 ± 14.5 (19–78)
Residential facility (yes/no)	27 (25%) / 81 (75%)
Smokers (yes/no)	55 (50.9%) / 53 (49.1%)
Coffee drinkers (yes/no)	52 (48.1%) / 56 (51.9%)
Study group 1	33 (30.6%)
Study group 2	22 (20.4%)
Study group 3	21 (19.4%)
Study group 4	32 (29.6%)
ODT (yes/no)	15 (13.9) / 93 (86.1%)
Olanzapine dose (mg per day)	15.4 ± 3.2 (10–20)
GAF score (baseline)	33.3 ± 5 (21–43)
GAF score (end of study)	61.5 ± 9.6 (28–80)
PANSS score (baseline)	100.7 ± 3.9 (90–109)
PANSS score (end of study)	85.5 ± 5.4 (73–104)
BMI (baseline) (kg/m²)	25.1 ± 3.2 (18.7–30.5)
BMI (end of study) (kg/m²)	26.0 ± 3.3 (19.3–39.7)
Glucose (mmol/L)	5.6 ± 0.9 (3.9–9.8)
Cholesterol (mmol/L)	5.9 ± 1.1 (3.8–9.2)
HDL cholesterol (mmol/L)	1.4 ± 0.3 (0.7–2.2)
LDL cholesterol (mmol/L)	3.6 ± 1.1 (1.5–6.5)
Triglycerides (mmol/L)	2.3 ± 1 (0.6–5.9)

Table 2. The change from the baseline (%)

Study group	GAF*	PANSS*
1	115.1 ± 35.7	-19.6 ± 3.1
2	91.1 ± 30.8	-15.3 ± 2.9
3	76.1 ± 29.8	-13.4 ± 4.4
4	64.7 ± 29.3	-11.3 ± 3.22

*$p < 0.001$, multivariable linear model

Table 3. Metabolic parameters of the patients according to the study groups

Parameter	Group 1	Group 2	Group 3	Group 4	p
Cholesterol (mmol/L)[1]	6.4 ± 1.2	5.9 ± 0.7	5.7 ± 1.1	5.4 ± 0.9	0.001
HDL cholesterol (mmol/L)[1]	1.3 ± 0.4	1.5 ± 0.2	1.4 ± 0.3	1.4 ± 0.4	0.080
LDL cholesterol (mmol/L)[1]	4.4 ± 1.1	3.6 ± 0.8	3.4 ± 0.9	2.3 ± 0.9	< 0.001
Glucose (mmol/L)[2]	5.8 (1.1)	5.6 (0.4)	5.5 (0.9)	5.6 (0.6)	0.323
Triglycerides (mmol/L)[2]	3.3 (2.2)	2.5 (0.7)	2.0 (1.1)	1.9 (0.5)	0.020
BMI change[1,3]	5.2 ± 3.3	2.9 ± 1.8	3.2 ± 2.6	1.7 ± 3.3	< 0.001

[1]mean ± standard deviation;
[2]median (interquartile range);
[3]percent from baseline

score percentage change from the baseline value ($p < 0.001$, F = 5.8, df = 10) and the PANSS total score ($p < 0.001$, F = 12.9, df = 10) (Table 2). Cigarette smoking and heavy coffee drinking (study group as a fixed variable) significantly diminished improvements in both GAF ($p < 0.001$, F = 10.0, df = 3) and PANSS total score ($p < 0.001$, F = 16.9, df = 10). The percentage changes of BMI from the baseline (a covariate) significantly influenced the change of the PANSS total score only ($p = 0.024$, F = 5.3, df = 3), in a negative direction (Pearson r = -0.454, $p < 0.001$). The patients' gender (a fixed factor) and age, and olanzapine daily dose (the covariates) did not affect the therapeutic response as assessed with either GAF or PANSS score changes ($p > 0.05$).

The median amount of coffee consumed per day was 4 cups (interquartile range 2, minimum 4, maximum 8). A significant correlation between the amount of coffee drinking and the change from the baseline for both GAF (Spearman ρ = -0.307, $p = 0.038$) and PANSS scores (Spearman ρ = 0.312, $p = 0.035$) was found. In regard to smoking, similar effects were not observed. The mean amount of tobacco smoked per day was 27 cigarettes (standard deviation 10, minimum 10, maximum 40), with no significant correlation with either GAF (Pearson r = -0.163, $p = 0.262$) or PANSS (Pearson r = 0.228, $p = 0.115$) score changes from the baseline.

The study patients who smoked and heavily drank coffee had significantly lower serum levels of cholesterol ($p = 0.001$, F = 5.6, df = 1, one-way analysis of variance), LDL cholesterol ($p < 0.001$, F = 11.9, df = 3, one-way analysis of variance) and triglycerides ($p = 0.020$, Kruskal–Wallis test), and had less increase in BMI ($p < 0.001$, F = 7.6, df = 3, one-way analysis of variance) (Table 3). However, these habits did not significantly influence the values of HDL cholesterol ($p = 0.080$, F = 2.3, df = 3, one-way analysis of variance) and glucose ($p = 0.323$, Kruskal–Wallis test).

DISCUSSION

The results of our study show that beneficial clinical response to olanzapine treatment is significantly decreased in patients who were smokers and heavy coffee consumers in comparison to abstinents. The effect of these life-style habits was synergistic, and it was more pronounced for tobacco than for coffee consumption. Different types of data distribution (skewed vs. normal) for coffee drinking and cigarette smoking could explain the observed difference in correlation analysis regarding the dose response. Weight gain had some predictive significance for positive olanzapine response. The cigarette smoking and heavy coffee intake decreased some adverse metabolic effects after the initiation of olanzapine treatment. Gender, age and olanzapine dose did not significantly influence the effects of either tobacco use or coffee drinking. To the best of our knowledge, no previous studies have been designed similarly to ours.

Our results are in accordance with fundamental facts in the field. Nicotine and caffeine have mainly beneficial effects in people with schizophrenia. They induce changes of the brain neurotransmitters, causing an improvement of disease symptoms such as the feeling of well-being (e.g. dopamine release) or cognition (e.g. nicotine receptors activation), with positive behavioral consequences (e.g. better structuring of daily activities), but also alleviating some of the side effects of drug treatment (e.g. drowsiness, extrapyramidal symptoms, dry mouth) [21, 22, 23]. On the other hand, it is known that cigarette smoking and heavy coffee

consumption strongly induce olanzapine-metabolizing cytochromes and decrease its plasma levels [15, 24, 25, 26]. At the same time, caffeine from coffee competitively inhibits olanzapine metabolism, as they share CYP1A2 as a common metabolizing enzyme [27, 28]. In our study, the proposed inducing effect seems to overcome the expected beneficial effects of nicotine and caffeine, as well as the metabolism inhibition by caffeine, resulting in diminished therapeutic response by almost one tenth to more than a quarter, depending on the rating assessment method.

It is well known that olanzapine has very profound metabolic adverse effects inducing dyslipidemia, glucose intolerance and weight gain [29]. In our study, smokers and heavy coffee drinkers had significantly lower serum levels of cholesterol and triglycerides, but also a lower increase in BMI without significant influence on glucose concentrations. The decrease of olanzapine blood concentration, most probably due to PAHs from cigarette smoke and coffee, could be considered a probable mechanism. In addition, there is a possibility that other factors, not identified in our research, could modulate the metabolic status of our patients. The patient's individual properties could cause particular metabolic patterns [30], as described in a case of olanzapine-induced dyslipidemia and hyperglycemia without an increase in weigh [31].

The results of our study should be interpreted considering several limitations. Moderate sample size and short study duration could decrease the power for identification of other important factors, which could have the effects of a lesser magnitude or be delayed, or could induce a compensatory response later in the course of treatment. In addition, we did not measure olanzapine blood concentration, thus only assumption about exact mechanism of smoking and heavy coffee drinking on the drug's pharmacokinetics, based on current, theoretical knowledge in the field, could be made. Finally, we did not perform an analysis of genetic polymorphism, which could affect pharmacokinetics and pharmacodynamics of olanzapine and, consequently, modulate its efficacy and safety. Therefore, to confirm our findings, additional studies are necessary.

CONCLUSION

Our study showed that cigarette smoking and heavy coffee drinking, frequent habits of patients with schizophrenia who were treated in clinical routine practice, affect the clinical response to olanzapine. In these patients, therapeutic drug monitoring of olanzapine treatment and appropriate adjustment of the dosing regimen could be advisable.

NOTE

This paper is a part of the doctoral thesis titled "Effect of polymorphism and induction of gene of metabolising enzymes on clinical response of patients treated with olanzapine" by Branimir Radmanović.

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Утицај пушења цигарета и значајног конзумирања кафе на клинички одговор болесника лечених оланзапином

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САЖЕТАК

Увод/Циљ С обзиром на релативно сложен фармакокинетички профил оланзапина, очекује се да поједини лекови и нека једињења која се налазе у храни и пићу могу индуковати или ихибирати његов метаболизам.

Циљ студије је био да се испита утицај пушења и интензивнијег конзумирања кафе на клинички одговор болесника лечених оланзапином.

Методе У проспективну, интервентну, контролисану клиничку студију IV фазе укључено је 108 болесника са дијагнозом схизофреније. У зависности од пушења цигарета (n = 52) и интензивног конзумирања кафе (n = 55) дефинисане су четири субгрупе: непушачи и особе које не пију кафу (група 1), непушачи и особе које интензивно пију кафу (група 2), пушачи и особе које не пију кафу (група 3) и пушачи и особе које интензивно пију кафу (група 4). За евалуацију клиничког одговора коришћене су скале *PANSS* и *GAF*.

Резултати Почетни и коначни резултати скале *GAF* су били 33,3 ± 5 односно 61,5 ± 9,6, а резултати скале *PANSS* су били 100,7 ± 3,9 односно 85,5 ± 5,4. Промене на скалама GAF и PANSS од почетка до краја студије су биле 115,1 ± 35,7 односно -19,6 ± 3,1 (група 1), 91,1 ± 30,8 односно -15,3 ± 2,9 (група 2), 76,1 ± 29,8 односно -13,4 ± 4,4 (група 3) и 64,7 ± 29,3 односно -11,3 ± 3,22 (група 4), чинећи значајну разлику субгрупа за обе скале (*p* < 0,001). Пушење и интензивније конзумирање кафе значајно и независно су смањили побољшање исказано и у GAF и у укупним *PANSS* (*p* < 0,001) скоровима. Промене *BMI* у односу на почетак истраживања значајно су утицале на промену *PANSS* укупног резултата (*p* = *n.s.*) у негативном смеру (*r* = -0,454, *p* < 0,001).

Закључак Пушење и интензивно конзумирање кафе утицали су на терапијске ефекте оланзапина код болесника оболелих од схизофреније у свакодневној клиничкој пракси.

Кључне речи: схизофренија; антипсихотици; кафа; употреба дувана