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Original Article

Changes in Plasma Clozapine Levels after Smoking Cessation in Japanese Inpatients with Schizophrenia: A Retrospective Cohort Study

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Although reported for Caucasians, changes in plasma clozapine levels after smoking cessation in East Asians remain unclear. We here investigated plasma clozapine levels before and after smoking cessation in Japanese inpatients with schizophrenia. We conducted a retrospective chart review of 14 inpatients with schizophrenia who were being treated with clozapine between June 1, 2019, and July 31, 2019 and who were smokers as of July 1, 2019, the day on which a smoking ban was instituted in the tertiary public psychiatric hospital. The primary outcome was individual differences in plasma clozapine levels between before and after the smoking ban, which were compared using paired *t*-tests. The mean plasma clozapine level was significantly increased, by 213.4 ng/mL (95% CI 119.9-306.8; $p<0.01$) or 53.2%. Four of the 14 inpatients experienced clinically significant side effects, such as myoclonus, drooling, and amnesia, due to the development of high plasma clozapine levels. Our findings indicated that close monitoring of plasma clozapine levels before and after smoking cessation and prior dose adjustment of clozapine may be necessary, to prevent a significant risk of developing high plasma clozapine levels, even in Japanese patients.

Key words: Asian, clozapine, schizophrenia, smoking

Clozapine is the most effective antipsychotic drug for treatment-resistant schizophrenia [1,2]. About 70% of clozapine is metabolized by cytochrome P-450 1A2 (CYP1A2) [3]. The major metabolite of clozapine is norclozapine (N-desmethylclozapine) [4]. Polycyclic aromatic hydrocarbons produced by smoking induce CYP1A2 activity, increasing the metabolism of clozapine [5] and decreasing plasma clozapine levels [6]. Conversely, smoking cessation increases plasma clozapine levels and may cause drug-related side-effects [7,8].

Current smoking rates among patients with schizophrenia are higher than in the general population, reaching 60% in some patient populations [9,10]. High rates of current smoking in patients with schizophrenia contribute significantly to early deaths from ischemic heart disease and cancer [11]. Encouraging patients with schizophrenia to quit smoking is important, particularly given that 70% of patients with schizophrenia who are current smokers report an interest in quitting smoking [12]. However, current smokers with schizophrenia taking clozapine should be carefully managed because there is a significant risk of developing high plasma clozapine levels after smoking cessation [13].

Studies investigating the effects of smoking cessation

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on plasma clozapine levels in individuals have been limited to those from Europe and the United States. A retrospective cohort study in the United States reported a 72% increase in plasma clozapine levels in individuals before and after smoking cessation [14]. Another retrospective cohort study in the United Kingdom showed that the proportion of patients with plasma clozapine levels ≥ 1000 ng/mL increased from 4.2% to 41.7% from before to after smoking cessation [15].

An inter-ethnic comparison study showed that the weight-adjusted maintenance clozapine dose in Caucasians was nearly twice that of Asians, with the plasma clozapine levels being similar in the two ethnic groups [16]. Such differences in dose requirement may indicate essential ethnic differences in the pharmacokinetics of clozapine [16]. Nevertheless, the individual changes in plasma clozapine levels with smoking cessation have not yet been reported in an East Asian population.

Aims of the study. In this retrospective cohort study, we aimed to investigate the individual changes in plasma clozapine levels from before to after the institution of a smoking ban in Japanese inpatients with schizophrenia.

Patients and Methods

Study design and setting. We conducted this retrospective cohort study in a single tertiary public psychiatric hospital in Okayama, Japan, which has a population of approximately 700,000 people. The hospital is a major public psychiatry hospital with 252 beds and consists of all closed wards.

Due to the partial revision of the Health Promotion Act in Japan, a hospital-wide smoking ban was introduced in our hospital on July 1, 2019, resulting in inpatients no longer being able to smoke anywhere on our hospital site. Before implementing this ban, a smoking area was provided in our hospital, where inpatients were allowed to smoke freely.

To adjust the dose of clozapine precisely, we measured plasma clozapine levels in all smoking inpatients who were taking clozapine before and after the smoking ban. In addition, we monitored patients for the potential side effects of clozapine using the Glasgow Antipsychotic Side-effects Scale for Clozapine (GASS-C) score to identify side effects as early as possible.

Participants. We included all inpatients with schizophrenia taking clozapine who were smokers as of July 1, 2019, the day on which the smoking ban at the Okayama Psychiatric Medical Center commenced. We excluded patients for any of the following reasons: (1) age < 18 years; (2) allowed to go out alone voluntarily; (3) clinically significant changes in clozapine dose per day between before and after the smoking ban (> 50 mg difference in clozapine dose per day); or (4) refused the use of their data for this study.

Data collection. We retrospectively collected the following data from the included patients' medical records between June 1, 2019, and July 31, 2019: age, sex, body mass index (BMI), 18-item Brief Psychiatric Rating Scale (BPRS) score [17] with each item rated from 1 (absent) to 7 (extremely severe), number of cigarettes smoked per day, caffeine intake per day, whether nicotine replacement treatment (NRT) was prescribed, clozapine-related side-effects, clozapine dose per day, plasma clozapine levels, plasma norclozapine levels, and GASS-C scores.

The GASS-C is a self-reported scale specific for the subjective side effects of clozapine during the past week. It consists of 16 questions answered with the following responses: 0 — Never; 1 — Once; 2 — A few times; and 3 — Every day. The total GASS-C score is calculated by summing the scores for each item, and ranges from 0 to 48. In the original GASS-C [18], the total GASS-C score is denoted as follows: 0-16 = absent/mild side-effects, 17-32 = moderate side-effects, and 33-48 = severe side-effects. The Japanese version of the GASS-C was used, which is a recognized reliable scale for assessing clozapine-related side effects [19].

Outcome measurements. The primary outcome was individual differences in plasma clozapine levels between before and after the smoking ban. The secondary outcomes were individual differences in plasma norclozapine levels, norclozapine/clozapine ratios, and the respective and total GASS-C scores between before and after the smoking ban.

We collected blood samples (10 mL) from patients in EDTA-2Na-containing tubes at an average of 12 ± 2 h after clozapine intake [20, 21]. Then, we centrifuged samples at 3,000 g for 10 min, and the plasma was collected and stored at −20°C until the assay, which was conducted within a week [22, 23]. Plasma clozapine and norclozapine levels were assessed by high-performance liquid chromatography (HPLC) with ultraviolet detection at 254 nm, modified from the analytical

method of Novartis, with loxapine as the internal standard. A fluorinated silica-gel-based column (WAKOPAK® Fluofix; Wako Pure Chemical Industries Ltd., Osaka, Japan) was used as the solid phase. The mobile phase consisted of acetonitrile and acetate buffer (50 : 50). The extraction recoveries were more than 85%. The inter- and intra-assay variances were less than 5%. The interday and intraday coefficients of variations were less than 11%. The standard curves were linear in the range of 100-2,000 ng/mL. This assay was not disturbed by routine psychotropic drugs or other drugs. All reagents used were of HPLC grade.

Statistical analysis. We calculated descriptive statistics for continuous and categorical variables of the baseline characteristics and outcomes of the subjects. We also performed paired *t*-tests to assess individual differences in clozapine dose per day, plasma clozapine levels, norclozapine levels, norclozapine/clozapine ratios and the total GASS-C scores between before and after the smoking ban. The respective GASS-C scores were non-normally distributed, and the nonparametric Wilcoxon signed-rank test was performed. The statistical tests were two-tailed and a 95% confidence interval was calculated. We conducted all statistical analyses using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a visual user interface for R (The R Foundation for Statistical Computing, version 3.6.1) [24]. Concretely, EZR is an improved version of R commander (version 2.6-2) designed to add statistical functions commonly used in biological statistics.

Ethics. This study protocol was approved by the institutional review board of our hospital, which permitted the inclusion of participants who did not actively reject the use of their data for this study.

Results

There were 17 inpatients with schizophrenia taking clozapine who were smokers as of July 1, 2019, the day on which the smoking ban at our hospital commenced. We excluded a patient who was allowed to go out alone voluntarily and two patients who had clinically significant changes in clozapine dose per day between before and after the smoking ban (>50 mg difference in clozapine dose per day). Consequently, we included 14 inpatients in the final analysis; none of these patients had any missing clinical data (Fig. 1). Table 1 presents the baseline characteristics of the subjects.

Table 2 presents individual differences in clozapine dose per day, plasma clozapine levels, plasma norclozapine levels, norclozapine/clozapine ratios and the total GASS-C scores between before and after the smoking ban. The mean increase in plasma clozapine level was 213.4 ng/mL (95% CI 119.9-306.8; $p<0.01$) (SD, 161.9; range, −17 to 629) or 53.2% (95% CI 30.5-75.9; $p<0.01$) (SD, 39.2; range, −3.0 to 123.8). The mean increase in plasma norclozapine level was 62.7 ng/mL (95% CI 33.5-92.0; $p<0.01$) (SD, 50.7; range, −10 to 143) or 27.7% (95% CI 16.9-38.5; $p<0.01$) (SD, 18.7;

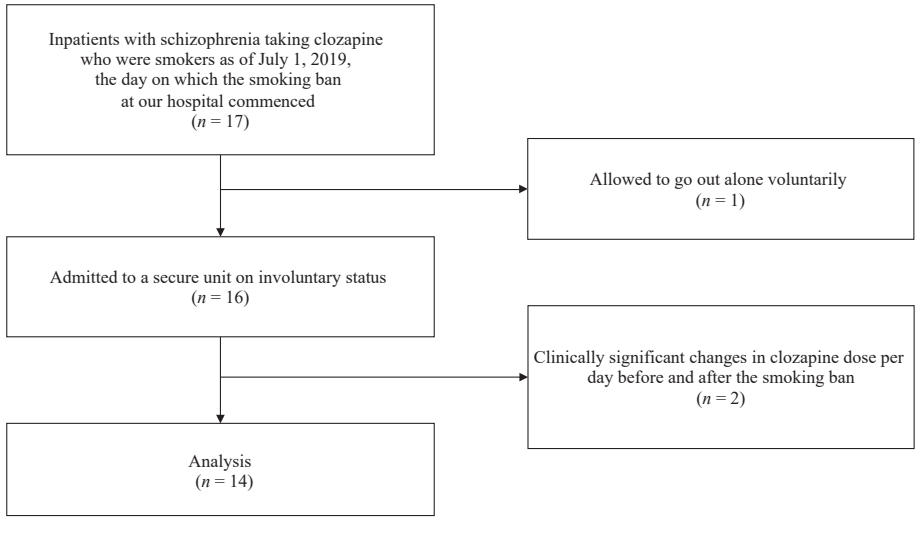

Fig. 1 Flow diagram of the patients.

Table 1 Baseline characteristics of the subjects

	n = 14
Age (years), mean (SD)	49.1 (10.8)
Sex (male), n (%)	13 (92.9)
BMI (kg/m^2), mean (SD)	24.0 (2.0)
BPRS score, mean (SD)	67.6 (19.8)
NRT prescribed, n (%)	3 (21.4)
Number of cigarettes smoked per day, mean (SD)	13.6 (9.6)
Median	10
Range	3–30
Interquartile range	5–20
Caffeine intake (mg/day), mean (SD)	58.2 (105.5)
Median	0
Range	0–300
Interquartile range	0–60
Number of days until collecting blood samples after the smoking ban, mean (SD)	11.7 (4.1)

SD, standard deviation; BMI, body mass index; BPRS, 18-item Brief Psychiatric Rating Scale; NRT, nicotine replacement treatment.

Table 2 Clozapine dose, clozapine level, norclozapine level, norclozapine/clozapine ratio and the total GASS-C score before and after the smoking ban

	Preban	Postban	t*	P value†
Clozapine dose (mg/day), mean (SD)	353.6 (154.7)	355.4 (153.5)	−0.322	0.75
Clozapine level (ng/mL), mean (SD)	486.2 (211.7)	699.6 (236.4)	−4.932	< 0.01
Norclozapine level (ng/mL), mean (SD)	250.8 (103.0)	313.5 (116.9)	−4.632	< 0.01
Norclozapine/clozapine ratio, mean (SD)	0.55 (0.20)	0.46 (0.14)	3.615	< 0.01
Total GASS-C score, mean (SD)	13.4 (7.2)	15.2 (8.7)	−2.160	0.05

SD, standard deviation.
*Student's t-test for paired samples, †Preban versus postb

range, −3.6 to 55.8). The metabolic ratio of clozapine, which was expressed as a norclozapine/clozapine ratio, was also significantly different ($t = 3.615$, $p < 0.01$). There was no significant difference in the total GASS-C scores.

Table 3 presents the respective GASS-C scores before and after the smoking ban. There were no significant differences in the respective GASS-C scores.

Each subject's characteristics, clozapine dose and plasma clozapine level before and after the smoking ban are shown in Table 4.

Discussion

Main findings. To our knowledge, no previous study has investigated the individual changes in plasma clozapine levels and GASS-C scores between before and after smoking cessation in Japanese patients with schizophrenia who were taking clozapine. In this study, the mean plasma clozapine level was significantly increased by 213.4 ng/mL, or 53.2%. Similarly, the mean plasma norclozapine level significantly increased, while the mean norclozapine/clozapine ratio significantly decreased. The total GASS-C score increased, although not significantly, and there were no significant changes in the respective GASS-C scores.

Comparison with previous studies. The mean increase of 53.2% in plasma clozapine levels in the Japanese population shown in the present study was smaller than that reported in studies conducted in the United States and the United Kingdom [14, 15]. Meyer [14] and Cormac *et al.* [15] reported that plasma clozapine at the individual level increased by 72% and 80%, respectively. In contrast, a retrospective cohort study at the Hawaii State Hospital reported that plasma clozapine at the individual level increased by 45.6% in a pop-

Table 3 Wilcoxon signed-rank test on the respective GASS-C scores before and after the smoking ban

		Preban	Postban	*P* value †
1	"I felt sleepy during the day", median (IQR)	2.5 (2.0–3.0)	3.0 (2.0–3.0)	0.35
2	"I felt drugged or like a zombie", median (IQR)	2.0 (0.0–3.0)	2.0 (0.0–3.0)	1.00
3	"I felt dizzy when I stood up or have fainted", median (IQR)	0.5 (0.0–1.8)	0.5 (0.0–2.0)	0.83
4	"I have felt my heart beating irregularly or unusually fast", median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.00
5	"I have experienced jerking limbs or muscles", median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.8)	0.35
6	"I have been drooling", median (IQR)	2.5 (0.3–3.0)	3.0 (2.0–3.0)	0.17
7	"My vision has been blurry", median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.00
8	"My mouth has been dry", median (IQR)	0.0 (0.0–1.8)	0.0 (0.0–1.0)	1.00
9	"I have felt sick (nauseous) or have vomited", median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.8)	0.37
10	"I have felt gastric reflux or heartburn", median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.8)	0.17
11	"I have had problems opening my bowels (constipation) ", median (IQR)	2.0 (1.0–2.0)	1.0 (0.3–2.0)	0.17
12	"I have wet the bed", median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.00
13	"I have been passing urine more often", median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–2.0)	0.22
14	"I have been thirsty", median (IQR)	1.0 (0.0–3.0)	1.0 (0.0–3.0)	1.00
15	"I have felt more hungry than usual or have gained weight", median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.77
16	"I have been having sexual problems", median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	NA

GASS-C, Glasgow Antipsychotic Side-effects Scale for Clozapine; IQR, interquartile range.
† Preban versus postban.

Table 4 Each subject's characteristics, clozapine doses and plasma clozapine levels before and after the smoking ban

Age (years)	Sex	BMI (kg/m^2)	Number of Cigarettes smoked per day	Caffeine intake (mg/day)	Preban clozapine dose (mg/day)	Preban clozapine level (ng/mL)	Postban clozapine dose (mg/day)	Postban clozapine level (ng/mL)	Increase in clozapine level (%)	Clinically significant side effects due to development of high plasma clozapine levels
46	F	21.2	20	0	600	450	600	606	34.7	None
47	M	25.8	5	300	450	675	450	775	14.8	None
56	M	26	30	60	250	359	250	540	50.4	None
27	M	22.4	30	60	550	257	600	497	93.4	None
45	M	23.3	10	0	250	558	250	626	12.2	None
33	M	21.7	5	0	200	295	225	501	69.8	None
57	M	24.3	5	60	75	246	100	414	68.3	None
56	M	27.2	20	35	350	641	350	952	48.5	Amnesia
55	M	23.4	3	300	300	568	275	551	−3.0	None
57	M	23.9	10	0	475	591	450	897	51.8	Drooling
63	M	26.3	20	0	150	304	150	474	55.9	None
41	M	25.4	20	0	400	339	400	736	117.1	None
62	M	23.1	10	0	450	508	450	1,137	123.8	Amnesia
42	M	21.3	3	0	450	1,016	425	1,088	7.1	Myoclonus

F, female; M, male; BMI, body mass index.

ulation approximately half of which were Asian individuals [25]. The results of the present study appear to be similar to those of this Hawaiian study. On the other hand, no study has yet investigated GASS-C scores from before to after smoking cessation in a secure psychiatric unit.

Possible explanations and implications. Ethnic differences in CYP1A2 metabolic activity may explain the smaller increases in plasma clozapine levels in the Japanese population after smoking cessation compared to the increases in Caucasians. A previous study found that plasma clozapine levels were 30-50% higher in 162 patients with schizophrenia in Taiwan than in Caucasian patients, despite the use of similar drug doses [26]. Another previous study showed that the mean daily dose of clozapine in Chinese patients with

schizophrenia was lower than that reported in the United States; however, the mean plasma clozapine level in Chinese patients was higher than that in the United States [27]. These studies suggest that there are significant ethnic differences in the pharmacokinetics of clozapine between Caucasians and Asians. Asians have also been reported to have a lower metabolism of clozapine, which is expressed as a norclozapine/clozapine ratio, compared to Caucasians [16]. This ratio is associated with CYP1A2 activity [28]. Therefore, the decreased clozapine metabolism in Asians may reflect a decrease in CYP1A2 activity, which has been previously reported in Asians [29]. In Caucasians, the CYP1A2*1F (−163C > A) variant has been linked to an increased induction in CYP1A2 activity by smoking [30]. Another study showed that the CYP1A2*1F was linked to increased induction of CYP1A2 activity by smoking in Swedes, but not in Koreans [31]. These results suggest that there is a significant ethnic difference in the pharmacokinetics of clozapine between Asians and Caucasians, and that the effect of smoking on the induction of CYP1A2 enzymatic activity is weaker in Asians than in Caucasians. Therefore, it can be inferred that plasma clozapine levels do not increase as markedly in the Japanese population as in Caucasians upon smoking cessation.

Nevertheless, the changes in plasma clozapine levels observed in our study should not be underestimated, because a 53.2% (SD, 39.2; range, −3.0 to 123.8) increase in plasma clozapine levels reflects a sizeable change. Two of the 14 inpatients in this study had a more than two-fold increase in plasma clozapine levels. Four inpatients experienced clinically significant side effects due to the increased plasma clozapine levels: myoclonus in one patient, increased drooling in one patient, and amnesia in two patients. Thus, in order to prevent drug side-effects after smoking cessation, it is advisable to measure plasma clozapine levels before and after smoking cessation and to reduce the daily doses of clozapine in advance, taking into account the response and tolerability. A previous meta-analysis also recommended that the clozapine dose should be reduced by 50% in non-smokers compared to smokers in order to maintain equivalent plasma clozapine levels [32].

In this study, there was no significant difference in the total GASS-C score, although there was an upward trend. Furthermore, the increase in the total GASS-C score was about two points, and none of the respective GASS-C scores exhibited significant variation. This suggests that the increase in plasma clozapine levels after smoking cessation cannot be adequately inferred from an assessment of clinical side effects alone. However, because of the small sample size, these results need to be interpreted cautiously.

Limitations. This study had several limitations, particularly with respect to the small sample size and its non-standardized data. This was a single-center study, which might limit the generalizability of our findings. The baseline characteristics of this study, including age and sex, are inconsistent with those of a previous cross-sectional study on clozapine safety and use based on Japanese national data [33]. Additionally, the small sample size might have resulted in a beta error with regard to the changes in the respective and total GASS-C scores. Due to the insufficient sample size, we could not examine the robustness of our results in various subgroups such as, for example, caffeine users. Moreover, this was a retrospective cohort study, which might limit the internal validity of our findings. Data collection was difficult to standardize, and the timing of testing of plasma levels for the cohort was not uniform.

In conclusion, our findings revealed that the mean plasma clozapine level was significantly increased, by 213.4 ng/mL or 53.2%, from before to after the smoking ban in Japanese inpatients with schizophrenia who were taking clozapine. Although the degree of increase was not as great as reported for Caucasians, the increase was sizeable. Therefore, in order to avoid a significant risk of developing high plasma clozapine levels, close monitoring of plasma clozapine levels before and after smoking cessation, and prior dose adjustment of clozapine may be necessary.

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