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Circadian patterns of hallucinatory experiences in patients with schizophrenia: Potentials for chrono-pharmacology☆

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ABSTRACT

The objective of this study was to investigate possible circadian pattern of psychotic symptoms in patients with schizophrenia, which could be reflected on the dosing schedule/regimen, i.e. chrono-pharmacology. Patients with schizophrenia (ICD-10) who reported having auditory hallucination, receiving monotherapy with risperidone, olanzapine or paliperidone for at least two weeks were included. The subjects were provided a diary and asked to record the time and duration of auditory hallucinations during the eight time periods (i.e. 00:00–03:00, 03:00–06:00, 06:00–09:00, 09:00–12:00, 12:00–15:00, 15:00–18:00, 18:00–21:00, and 21:00–24:00). In the diary, times of medication doses and sleep were also recorded. Time and degree of peak and trough dopamine D_2 receptor blockade with antipsychotics were estimated from 2 sparsely collected plasma drug concentrations. The prevalence and duration of auditory hallucinations were statistically examined among the eight time periods, respectively. Forty-nine patients participated in this study (mean ± SD age, 50.7 ± 14.8 years; 36 men (73.5%); 34 inpatients (69.4%)). Auditory hallucinations occurred most frequently and lasted for the longest duration in the period of 18:00–21:00 (75.5% (37/49) and 1.37 ± 1.67 h). This happened despite the fact that the difference in D_2 receptor occupancy between the peak and trough was less than 2%, indicating a stable drug delivery. Since the dopamine D_2 receptor blockade by antipsychotics was stable, the nocturnal circadian pattern found in this study may reflect intrinsic dopaminergic fluctuation or generally quieter environments at night. These circadian patterns may be considered to devise individualized treatment approach in the context of "chrono-pharmacology" for patients with schizophrenia.

1. Introduction

Circadian rhythm is vital to human being; its association with symptomatic fluctuations has been reported in a variety of physical as well as psychiatric conditions. For example, asthma attacks tend to get worse from midnight to early morning (Panzer et al., 2003) while patients with hypertension experience the peak of blood pressure in the morning and early evening (Hermida et al., 2001). Subarachnoid hemorrhage has been found to occur more frequently in the morning (Feigin et al., 2001). In the treatment of physical conditions, such circadian patterns have often been taken into consideration to devise effective dosing schedule, which is interpreted in the context of "chrono-pharmacology". This approach aims to increase the exposure to medication during or before the time of symptom worsening in order to mitigate or prevent these symptoms. On the other hand, the circadian rhythm has not garnered wide attention in the field of psychiatry with some notable exceptions such as exacerbation of depressive symptoms in the morning (Murray, 2007) and delirium at night (Lipowski, 1987).

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To the best of our knowledge, there has been no study that investigated the circadian pattern of psychotic symptoms in patients with schizophrenia. If this circadian pattern is revealed, the concept of chrono-pharmacology will be all the more relevant to the treatment of schizophrenia. In this study, we investigated fluctuations in auditory hallucination within a day in patients with schizophrenia who were receiving antipsychotic monotherapy with oral risperidone, paliperidone, or olanzapine. Dopamine D_2 receptor blockade levels with antipsychotics that were estimated from plasma drug concentrations were also evaluated to assess drug exposure. We herein focused on auditory hallucinations since they are easily reported by the patients and quantified.

2. Methods

2.1. Subjects and settings

This study was conducted at Shimofusa Psychiatric Medical Center, Inokashira Hospital, Minami-Hannou Hospital, Ohizumi Hospital, Asakadai Mental Clinic, and Kaido Hospital in Japan. The study was approved by the institutional review board at all participating sites, and prior to study entry subjects provided written informed consent after receiving detail information about the protocol. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

In- and outpatients aged 20 or older who fulfilled the following criteria were invited to participate in this study(Kane et al., 2003): diagnosis of schizophrenia according to the International Classification of Diseases, the 10th edition (ICD-10) (World Health Organization, 1992) (Kane et al., 2003) having auditory hallucinations as assessed subjectively by patients themselves as well as objectively by their physician in charge (Kane et al., 2003),receiving stable treatment with antipsychotic monotherapy with oral risperidone, paliperidone, or olanzapine for at least two weeks, and (DeVane et al., 2002) being capable of providing informed consent. We included the subjects who were receiving such pharmacotherapy since the estimation model for dopamine D_2 receptor occupancy levels from peripheral plasma antipsychotic concentrations were only available for these medications as described below (Nakajima et al., 2016; Tsuboi et al., 2015; Uchida et al., 2011b, 2012). Patients who had unstable physical conditions judged by their treating psychiatrists were excluded.

2.2. Assessments

The subjects were provided a diary and asked to record the time and duration of auditory hallucinations during the eight time periods (i.e. 00:00–03:00, 03:00–06:00, 06:00–09:00, 09:00–12:00, 12:00–15:00, 15:00–18:00, 18:00–21:00, and 21:00–24:00) for three consecutive days. In the diary, times of medication doses and sleep were also recorded. If they experienced auditory hallucinations for two or three days, the result from the earliest day was used for the analysis. The following information was also collected: medications prescribed, ethnicity, sex, age, age at onset, duration of antipsychotic treatment, and treatment setting (i.e. inpatient or outpatient), height, weight, and smoking status. Symptomatology and drug side effects were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Global Assessment of Functioning (GAF) (Endicott et al., 1976), the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970), the Barnes Akathisia Rating Scale (Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS) (Guy and Cleary, 1976). In this study, we used population pharmacokinetic model for estimation of peak and trough plasma antipsychotic concentrations as detailed below. One of the major advantages of population pharmacokinetic model over the traditional pharmacokinetic model is that this approach allows the use of sparsely and randomly sampled data, compared to the traditional method in which only intensive, precisely timed data is collected and used (Ng et al., 2009). In the present study, we therefore collected samples at any two given points in time for the measurement of plasma antipsychotic concentrations. Dates and times of doses for the past 24 h and blood draw were also recorded for population pharmacokinetic analysis.

2.3. Estimation of dopamine D_2 receptor occupancy

Using the two plasma concentrations of risperidone, paliperidone or olanzapine, plasma antipsychotic concentrations at peak and trough and times of peak and trough concentrations were calculated for each individual, using the established population pharmacokinetic models and extracting the Empirical Bayes Estimates for the pharmacokinetic parameters from each of these individuals (Sheiner et al., 1977). The nonlinear mixed-effect models for risperidone and olanzapine were previously established using the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) data (Bigos et al., 2008; Feng et al., 2008). The precision and reliability of this estimation has been previously confirmed (Tsuboi et al., 2015; Uchida et al., 2012). Peak and trough plasma concentration for paliperidone were calculated using the model available in literature (Korell et al., 2017). Since our aim was to examine differences in occurrence and duration of auditory hallucinations, we had to exclude the sleep period in which the subjects did not experience any auditory hallucinatory symptom. Therefore, if estimated peak or trough concentrations fell in the sleep period, the highest or lowest concentrations in the awake period were used for further analyses. Using the estimated plasma concentrations, corresponding D_2 receptor occupancy levels were estimated, using the model that we developed (Nakajima et al., 2016; Uchida et al., 2011b). Briefly, D_2 receptor occupancy levels for risperidone, paliperidone, and olanzapine were estimated by incorporating the estimated plasma concentration of risperidone and 9-OH-risperidone, 9-OH-risperidone, and olanzapine, respectively, into the following one-site binding model: occupancy (%) = a × [plasma level/(plasma level + ED_{50})], where a is the maximum receptor occupancy attributable to the antipsychotic drug and ED_{50} is the estimated plasma concentration of the antipsychotic drug associated with 50% of receptor occupancy, which was obtained in the systematic review and pooled analysis (olanzapine: a = 90.7%, ED_{50} = 7.1 ng/mL; risperidone active moiety: a = 88.0%, ED_{50} = 4.9 ng/mL).

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS Version 25.0 (IBM, New York, USA). A chi-squared test was conducted to examine the prevalence of auditory hallucinations among the eight time periods. In addition, we also conducted a chi-squared test after excluding the time periods in which the subjects were sleeping. Analysis of variance (ANOVA) was used to examine the duration of auditory hallucinations among the eight time periods. To exclude the effects of sleep on the results of this analysis, we also performed ANOVA after excluding the time periods in which the subjects were sleeping. The frequency and the duration of auditory hallucinations were compared between the time periods that included peak and trough drug concentration by using chi-squared tests and a paired *t*-test, respectively. A chi-squared test was conducted to examine the incidence of peak and trough concentrations, respectively, among the eight time periods.

3. Results

3.1. Subject characteristics

Recruitment took place between August 2014 and November 2017. Forty-nine subjects participated in this study. Of these, plasma sample

Table 1
Demographic and clinical characteristics of subjects.

Characteristics	Value (N = 49)
Age, years	50.7 ± 14.8
Male sex	36 (73.5)
Inpatient status	34 (69.4)
Duration of illness, years	23.9 ± 15.8
Duration of treatment, years	21.1 ± 16.1
Age at onset, years	26.4 ± 10.5
GAF	34.9 ± 9.6
PANSS total score	84.9 ± 20.4
Positive scale score	21.9 ± 5.4
Negative scale score	22.1 ± 6.8
General psychopathology scale score	41.0 ± 11.5
Antipsychotics, mg/day	
Risperidone (n = 11)	4.7 ± 3.2
Paliperidone (n = 3)	14.9 ± 5.7
Olanzapine (n = 34)	9.0 ± 3.0

Values are shown as mean ± S.D. or n (%).
Abbreviations: GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale.

was not available in one subject. Baseline demographic and clinical characteristics were summarized in Table 1. Their mean age was in their early 50s, and the duration of illness was more than 20 years; this indicates that many of them suffered from chronic schizophrenia. The most frequently used antipsychotic drug was olanzapine (n = 34, 70.8%), followed by risperidone (n = 11, 22.9%) and paliperidone (n = 3, 6.25%), respectively. The most common dosing schedule was once at bedtime (n = 27, 55.1%) followed by once after dinner (n = 7, 14.3%), once after breakfast (n = 6, 12.2%), once each after breakfast and dinner (n = 4, 8.16%), once each after breakfast and at bedtime (n = 2, 4.1%), once each after lunch and at bedtime (n = 2, 4.1%), and once after lunch (n = 1, 2.0%).

3.2. Circadian pattern of auditory hallucinations

Auditory hallucinations occurred most frequently in the period of 18:00–21:00 (75.5%); this finding did not change even after the time periods of sleep were excluded (77.3) (Table 2). Also the duration of auditory hallucinations was the longest from 18:00 to 21:00 (1.37 ± 1.67 h); however, the analysis that was conducted for when excluding the time periods in which the subjects were sleeping, the statistically significant difference disappeared (Table 3).

3.3. Plasma antipsychotic concentrations and estimated D_2 receptor occupancy

Peak and trough drug concentrations were most frequently observed from 9:00–12:00 (n = 20 [41.7%]) and 18:00–21:00 (n = 29 [60.4%]) (Table 4). Plasma antipsychotic concentrations during the awake period were statistically significantly higher at peak than at trough in those receiving risperidone and olanzapine, respectively. The dopamine D_2 receptor occupancy levels were also significantly higher at peak than at trough (Table 5), but the numerical difference in D_2 receptor occupancy between them was less than 2%, indicating a very stable drug delivery.

4. Discussion

In the present study, we observed the nocturnal predominance of auditory hallucinations among patients with schizophrenia. This happened in spite of the fact that dopamine D_2 receptor blockade with ongoing antipsychotic treatment was very stable with an only 2% difference between peak and trough. Despite some limitations discussed below, these findings will help better understand symptomatology of schizophrenia and provide relevant scientific basis to devise individualized treatment approach for patients with schizophrenia,

Table 2
Occurrence of hallucinations in respective time periods.

	0:00–3:00	3:00–6:00	6:00–9:00	9:00–12:00	12:00–15:00	15:00–18:00	18:00–21:00	21:00–24:00	Statistics
Occurrence, % (n/N)	4.1 (2/49)	14.2 (7/49)	57.1 (28/49)	61.2 (30/49)	55.1 (27/49)	55.1 (27/49)	75.5 (37/49)	55.1 (27/49)	$\chi^2_{(7)} = 83.11$, $p < 0.001$
Occurrence when periods for sleeping were excluded, % (n/N)	n.a.[a]	50.0 (1/2)	59.3 (16/27)	61.2 (30/49)	55.1 (27/49)	55.1 (27/49)	77.3 (34/44)	14.3(1/7)	$\chi^2_{(7)} = 12.66$, $p = 0.0499$

[a] No subject was awake throughout the period of 0:00–3:00.

Table 3
Durations of hallucinations in respective time periods.

	0:00–3:00	3:00–6:00	6:00–9:00	9:00–12:00	12:00–15:00	15:00–18:00	18:00–21:00	21:00–24:00	Statistics
Duration, hours	0.04 ± 0.29	0.11 ± 0.36	1.07 ± 1.17	1.27 ± 1.26	1.09 ± 1.23	1.12 ± 1.26	1.37 ± 1.67	0.24 ± 0.45	$F_{(7,\ 384)} = 13.4$, < 0.001
Duration when periods for sleeping were excluded, hours	n.a.[a]	0.25 ± 0.35 (n = 2)	1.35 ± 1.28 (n = 27)	1.27 ± 1.26 (n = 49)	1.09 ± 1.23 (n = 49)	1.12 ± 1.26 (n = 49)	1.50 ± 1.64 (n = 44)	0.36 ± 1.33 (n = 7)	$F_{(6,\ 226)} = 1.18$, $p = 0.316$

Values are shown as mean ± S.D.
[a] No subject was awake throughout the period of 0:00–3:00.

including effective dosing regimen from the viewpoint of chrono-pharmacology.

4.1. Circadian patterns of auditory hallucinations

In this study, auditory hallucinations most frequently occurred between 6 p.m. and 9 p.m. while there were some variations among individuals. One potential explanation for this pattern is circadian rhythmicity of the dopaminergic function. Plasma concentration of homovanillic acid, a metabolite of dopamine, has been reported to reach the peak between midnight and 5 a.m. in patients with schizophrenia who were treated with placebo as well as healthy controls (Doran et al., 1990). Moreover, patients who were receiving fluphenazine showed the same pattern with a low amplitude (Doran et al., 1990). One animal experiment using rats that were exposed to a 12 h dark and 12 h light cycle for two weeks also showed an increase in dopamine under the dark condition in the striatum and nucleus accumbens (Castaneda et al., 2004). Such nocturnal activity in the dopaminergic system may more frequently cause positive symptoms at night. These levels likely start to rise already in the evening and most of the patients with schizophrenia sleep after 9 p.m., which may have led to our observation that the time period of 6 p.m.–9 p.m. was associated with the most frequent occurrence of auditory hallucinations.

Another possible reason may be related with generally quiet environment in the evening compared to the daytime. In a quiet setting, patients with schizophrenia may easily hear their 'inner voices' without significant distraction, as has been observed in nocturnal worsening of tinnitus (Probst et al., 2017). Thus, both biological and environmental factors seem to contribute to the circadian pattern of positive symptoms in patients of schizophrenia.

4.2. Potentials for chrono-pharmacology

Dopamine D_2 receptor occupancy levels estimated from plasma drug concentrations were significantly higher at peak than at trough; however, its numerical difference was less than 2%, indicating a very constant exposure to antipsychotic drugs. In the treatment of schizophrenia, dosing schedule of antipsychotics has conventionally aimed at assuring constant delivery of the drug as evidence shows that continuous blockade of dopamine D_2 receptors with antipsychotic drugs at 65–80% increases the chance of clinical response in the acute phase (Farde et al., 1995; Kapur et al., 2000; Uchida et al., 2011a). In the context of chrono-pharmacology, one potential treatment option would be to give the medication a few hours (i.e. t_{max}) before the time period in which psychotic symptoms, including auditory hallucinations, are expected to get worse. Moreover, it would be reasonable to reduce the exposure to antipsychotic drugs when those psychotic symptoms are less likely to happen. When effectiveness of this dosing strategy is examined, antipsychotic drugs with relatively short $t_{1/2}$ and t_{max} will be ideal.

4.3. Limitations

There are some limitations to be noted in the present study. First, there are other significant symptoms of schizophrenia such as negative symptoms and cognitive impairments, whose circadian rhythms were not evaluated in this study. Second, only patients who were treated with monotherapy with risperidone, paliperidone, or olanzapine were included in this study. Third, the striatal dopamine D_2 receptor occupancy was not measured by positron emission tomography but estimated by plasma drug concentrations. Finally, the participants were generally old, male, and inpatients and all Japanese, which may limit the generalizability of the results to other populations.

Table 4
Time periods of antipsychotics peak and trough concentrations.

	0:00–3:00	3:00–6:00	6:00–9:00	9:00–12:00	12:00–15:00	15:00–18:00	18:00–21:00	21:00–24:00	Statistics
Peak, n (%)	2 (4.2)	0 (0.0)	10 (20.8)	20 (41.7)	6 (12.5)	4 (8.3)	1 (2.1)	5 (10.4)	$\chi^2_{(7)} = 55.84$, $p < 0.001$
Trough, n (%)	0 (0.0)	1 (2.1)	7 (14.6)	1 (2.1)	2 (4.2)	0 (0.0)	29 (60.4)	8 (16.7)	$\chi^2_{(7)} = 127.63$, $p < 0.001$

Table 5
Antipsychotics plasma concentrations and estimated D_2 receptor occupancies at peak and trough during the awake period.

	Peak	Trough	p-value
D_2 receptor occupancy, %	76.32 ± 9.64	74.36 ± 10.54	$t_{(47)} = 4.08$, $p < 0.001$
Plasma drug concentration, ng/mL			
Risperidone (n = 11)	53.49 ± 36.05[a]	33.31 ± 23.66[a]	$t_{(10)} = 3.255$, $p = 0.009$
Paliperidone (n = 3)	32.46 ± 12.81[b]	31.85 ± 12.36[b]	$t_{(2)} = 2.093$, $p = 0.171$
Olanzapine (n = 34)	60.34 ± 36.23	55.02 ± 32.14	$t_{(33)} = 2.459$, $p = 0.019$

Values are shown as mean ± S.D.
[a] Risperidone plus 9-hydroxyrisperidone.
[b] 9-Hydroxyrisperidone.

4.4. Conclusion

The findings from this study suggest the presence of a circadian pattern in auditory hallucinations in patients with schizophrenia, in which they frequently occur in the evening. Dosing schedule to maximize the drug delivery during the time period with more frequent symptoms and minimize it outside such time period may theoretically be considered from a standpoint of chrono-pharmacology. Although this preliminary contention regarding dosing regimen has to be tested in prospective studies, such a dosing schedule has the potential to maximize the treatment efficacy and minimize side effects with antipsychotic treatment.

Contributors

Teruki Koizumi designed the study, recruited the subjects, analyzed the data, and wrote the first draft of the manuscript. Nikhil Sasidharan Pillai, Robert R. Bies, and Kimio Yoshimura analyzed the results. Takefumi Suzuki and Hiroyoshi Takeuchi designed the study, analyzed the results and wrote the manuscript. Masaru Mimura wrote the manuscript. Hiroyuki Uchida designed the study, recruited the subjects, analyzed the data, and wrote the first draft of the manuscript. All authors have made substantial contributions to the conception, participated in drafting the article or revising it critically for important intellectual content, and read and approved the final version of the manuscript.

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Conflicts of interest

Dr. Suzuki has received manuscript or speaker's fees from Astellas, Dainippon Sumitomo Pharma, Eli Lilly, Elsevier Japan, Janssen Pharmaceuticals, Kyowa Yakuhin, Meiji Seika Pharma, Novartis, Otsuka Pharmaceutical, Shionogi, Tsumura, Wiley Japan, and Yoshitomi Yakuhin, and research grants from Eisai, Mochida Pharmaceutical, and Meiji Seika Pharma within the past three years. Dr. Bies has received grant funding from Takeda Pharmaceuticals and served as an expert witness for Janssen Pharmaceuticals through Belmore Neidrauer LLP. Dr. Takeuchi has received speaker's honoraria from Meiji-Seika Pharma, Mochida, Otsuka, Sumitomo Dainippon Pharma, and Yoshitomi Yakuhin, and manuscript fees from Sumitomo Dainippon Pharma. Dr. Mimura has received speaker's honoraria from Daiichi Sankyo, Dainippon-Sumitomo Pharma, Eisai, Eli Lilly, Fuji Film RI Pharma, Janssen Pharmaceutical, Mochida Pharmaceutical, MSD, Nippon Chemipher, Novartis Pharma, Ono Yakuhin, Otsuka Pharmaceutical, Pfizer, Takeda Yakuhin, Tsumura, and Yoshitomi Yakuhin within the past three years. Also, he received grants from Daiichi Sankyo, Eisai, Pfizer, Shionogi, Takeda, Tanabe Mitsubishi and Tsumura within the past three years. Dr. Uchida has received grants from Eisai, Otsuka Pharmaceutical, Dainippon-Sumitomo Pharma, and Meiji-Seika Pharmaceutical; speaker's honoraria from Otsuka Pharmaceutical, Eli Lilly, Pfizer, Yoshitomi Yakuhin, Dainippon-Sumitomo Pharma, Meiji-Seika Pharma, and MSD; and advisory panel payments from Dainippon-Sumitomo Pharma within the past three years. Dr. Koizumi has nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.06.019.

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