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Brief report

Severe sleepiness and excess sleep duration induced by paroxetine treatment is a beneficial pharmacological effect, not an adverse reaction

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ABSTRACT

Background: Severe sleepiness and excess sleep duration, "Hypersomnia", induced by paroxetine treatment are generally considered adverse drug reactions, however, our experience indicates that patients with depressive disorder who experience "Hypersomnia" during paroxetine treatment have good clinical response. The aim of this study was to determine if "Hypersomnia" during paroxetine treatment is a beneficial pharmacological effect or an adverse drug reaction, and to investigate the impact of genetic polymorphisms on individual differences in the occurrence of "Hypersomnia" induced by paroxetine.
Methods: A consecutive series of 46 Japanese patients with depressive disorder were treated with paroxetine. Patients who complained of great drowsiness or who slept for more than 12-h per day over seven days were identified as having experienced "Hypersomnia". For the clinical improvement rates and genotype distribution of the circadian locomotor output cycles kaput (CLOCK), serotonin transporter and cytochrome P450 2D6 (CYP2D6), the group that showed "Hypersomnia" induced by paroxetine treatment and the group that did not show "Hypersomnia" were compared statistically.
Results: Patients who experienced "Hypersomnia" (17.4%) showed a significantly higher response rate at two weeks than did patients who did not experience "Hypersomnia" ($p=0.0127$). No significant association between the occurrence of "Hypersomnia" and genetic polymorphisms was found.
Limitations: We cannot exclude the risk of false positive errors due to the relatively small sample sizes.
Conclusions: "Hypersomnia" during paroxetine treatment for depression is a beneficial pharmacological effect, not an adverse drug reaction.

1. Introduction

Paroxetine, a selective serotonin reuptake inhibitor (SSRI), has been widely and successfully used in the treatment of major depressive disorder and anxiety disorders (Green, 2003). Although paroxetine has been shown to be safe and well-tolerated, much attention has been paid to several adverse reactions (Murata et al., 2010; Tanaka et al., 2008). Severe sleepiness and excess sleep duration sometimes occur in the early stage of the treatment with paroxetine (Papakostas, 2008), and they have commonly been regarded as adverse drug reactions (Winokur et al., 2001).

When patients complain of disturbance to their daily lives because of severe sleepiness or excess sleep duration, most doctors discontinue the drug and prescribe another antidepressant. However, our considerable clinical experience indicates that the severe sleepiness and excess sleep duration associated with paroxetine are transient and that the increased sleep duration normalizes in most of the patients as the symptoms of their depression improve.

Insomnia is the most common symptoms associated with depressive disorder (Thase, 1999; Tsuno et al., 2005). Based on our clinical experience as described above, we hypothesized that the severe sleepiness and excess sleep duration seen during paroxetine treatment may be an expression of a significant improvement in insomnia that indicates a therapeutic effect of paroxetine. Few studies have focused specifically on severe sleepiness or excess sleep duration caused by paroxetine or other SSRIs from the standpoint of therapeutic significance. This study was done to determine if severe sleepiness and excess sleep duration during paroxetine treatment is a beneficial pharmacological reaction or an adverse drug reaction.

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Additionally, our clinical experience indicates that there are individual differences in the occurrence of severe sleepiness and excess sleep duration during paroxetine treatment. Thase et al. (2005) estimated the incidence of somnolence during treatment with SSRIs to be 12%. However, the reasons for the individual differences in response to paroxetine treatment have not been clarified, and it is currently not possible to predict the occurrence of these symptoms before the start of treatment.

We speculate that the PK/PD profiles of paroxetine and circadian rhythm may contribute to the individual differences.

To investigate the significance of genetic polymorphisms on the occurrence of the severe sleepiness and excess sleep duration induced by paroxetine, we focused on a gene that has been shown to play an important role in regulating circadian rhythm and on the genes known to affect the PK/PD of paroxetine.

2. Methods

2.1. Participants and assessment

The participants were a series of 46 consecutive Japanese outpatients who were treated with oral paroxetine for more than 8 weeks. Written informed consent was obtained from each participant. All of the patients had DSM-IV diagnoses of major depressive disorder. The study design was in accordance with the principles of the Helsinki Declaration and was approved by the Ethics Committees of Kyushu University Hospital and the Faculty of Pharmaceutical Science, Fukuoka University.

In this study, patients who slept for more than 12 h/day over seven days were identified as having *"Hypersomnia"*. All patients were assessed at baseline and after 2, 4 and 8 weeks of paroxetine treatment for the therapeutic response using the 17-item Hamilton Rating Scale for Depression (HAM-D) and for the occurrence of *"Hypersomnia"* during paroxetine treatment. The other information's were shown in Supplementary Table 1.

2.2. Genotyping

Of the 46 participants, twenty-seven agreed with informed consent to participate in the pharmacogenetic study that included analysis of genetic polymorphisms. Genomic DNA was isolated from peripheral blood using the commercial kit (Qiagen). Genetic polymorphisms were analyzed by PCR or PCR-RFLP methods as described in Supplementary Table 2.

2.3. Statistics

Data analyses were done with StatView 5.0 (HULINKS). The statistical methods are described in Supplementary Table 3. The limit of significance was set to 0.05.

3. Results

Of the 46 participants, eight (17.4%) experienced *"Hypersomnia"* during paroxetine treatment, sleeping soundly for more than 12 h/day. The *"Hypersomnia"* lasted for an average of 5.6 ± 4.7 weeks (range 2.0–16.0). In all cases, the *"Hypersomnia"* gradually disappeared and the patients' sleep patterns became normal. At the point when normal sleep patterns became established, the patients' depressive symptoms were greatly improved or disappeared altogether. Supplementary Fig. 1 shows the case of a typical patient who experienced *"Hypersomnia"*.

Table 1 shows the demographic and clinical characteristics of patients with and without *"Hypersomnia"* during paroxetine treatment. As shown in Table 1, the patients with *"Hypersomnia"* showed a significantly higher HAM-D score improvement rate at

Table 1
Demographic characteristics, Hamilton rating scale for depression (HAM-D) score at baseline, HAM-D score improvement, responder, and remission rates of 46 patients with and without *"Hypersomnia"* during paroxetine treatment.

Demographic and clinical characteristics	*"Hypersomnia"* (+)	*"Hypersomnia"* (−)	Test static	*P*[a]
	(*N*=8)	(*N*=38)		
Sex [male (%)]	2 (25.0)	16 (42.1)	χ^2=0.25	0.453
Age [year; mean (s.d.)]	38.8 (12.8)	50.2 (19.3)	*U*=96.5	0.108
Maintenance dosage of paroxetine [mg/day; mean (s.d.)]	32.5 (7.1)	33.7 (10.8)	*U*=140.5	0.726
Use of psychotropic co-medication [Yes (%)]				
Anxiolytics	8 (100.0)	36 (94.7)	χ^2=0.00	>0.999
Hypnotics	5 (62.5)	23 (60.5)	χ^2=0.00	>0.999
Presence of sleep disorder at baseline [Yes (%)]	8 (100.0)	35 (92.1)	χ^2=0.00	>0.999
HAM-D score at baseline [mean (s.d.)]				
Total of 17-item version	23.9 (4.9)	23.9 (4.5)	*U*=151.0	0.977
Total of 14-item version (omitted the three items on insomnia)	19.9 (3.9)	19.4 (3.7)	*U*=146.5	0.873
17-item HAM-D score improvement rate [%; mean (s.d.)]				
Week 2	48.1 (20.1)	31.1 (20.6)	*U*=81.0	0.0396[b]
Week 4	69.6 (18.4)	56.3 (24.5)	*U*=108.5	0.207
Week 8	78.1 (20.5)	76.9 (21.0)	*U*=151.0	0.977
14-item HAM-D score improvement rate [%; mean (s.d.)]				
Week 2	41.8 (19.6)	25.8 (18.0)	*U*=82.0	0.0425[b]
Week 4	66.1 (21.2)	54.1 (24.2)	*U*=116.0	0.297
Week 8	76.3 (24.1)	75.3 (21.2)	*U*=151.0	0.977
Responder rate [responder (%)]				
Week 2	5 (62.5)	6 (15.8)	χ^2=5.57	0.0127[b]
Week 4	8 (100.0)	26 (68.4)	χ^2=1.98	0.0898
Week 8	7 (87.5)	32 (84.2)	χ^2=0.00	>0.999
Remission rate at week 8 [remission (%)]	6 (75.0)	27 (71.1)	χ^2=0.00	>0.999

[a] Nominal *p* value by Fisher's exact test or Mann–Whitney *U* test.
[b] 5% Statistical significance.