Asian Journal of Psychiatry 36 (2018) 20–24

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

A survey of the effects of ramelteon on benzodiazepine-dependence: Comparison between a ramelteon add-on group and a continuous benzodiazepine administration group

Keiko Naono-Nagatomo[a,*], Hiroshi Abe[b], Ryuji Araki[c], Hideki Funahashi[a], Ryuichiro Takeda[d], Hiroshi Taniguchi[e], Yasushi Ishida[a]

[a] Division of Psychiatry, Department of Clinical Neuroscience, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan
[b] School of Psychological Science, Health Science University of Hokkaido, Tobetsu, Japan
[c] Department of Psychiatry, Sansyuwakitaoka Hospital, Kagoshima, Japan
[d] Health Care and Security Center, University of Miyazaki, Miyazaki, Japan
[e] Department of Psychiatry, Dojinkai Taniguchi Hospital, Japan

ARTICLE INFO

Keywords:
Benzodiazepine
Dependence
Insomnia
Global assessment of functioning
Pittsburgh sleep quality index
Ramelteon

ABSTRACT

In general, long-term benzodiazepine hypnotics are prescribed for patients in whom it is difficult to reduce benzodiazepine hypnotics. Unlike benzodiazepine receptor (BZ)-mediated sleep agents, ramelteon induces quasi-natural physiological sleep owing to its mechanism of action. We conducted a survey of ramelteon and BZ-dependence in patients with insomnia. Study subjects were patients with insomnia (42 cases), who were divided into a ramelteon group (22 cases; administered 8 mg/day of ramelteon before sleep in addition to BZ) and a control group (20 cases; continually administered only BZs), with a mean disease duration of 11.3 ± 9.6 years. All data were analyzed using two-way repeated measures analysis of variance. A significant improvement in scores at Week 16 over those of Week 0 was observed in the ramelteon group when a questionnaire concerning BZ-dependence and withdrawal symptoms was used. A significant improvement in scores at Week 16 from those at Week 0 was also observed in the Pittsburgh Sleep Quality Index excerpt and in the Global Assessment of Functioning in the ramelteon group. The Wilcoxon rank-sum test showed that the number of concomitantly used BZ hypnotics decreased significantly in the ramelteon group after Week 16, while no such change was observed in the control group. Thus, by adding ramelteon to therapy for patients with long-term insomnia, we were able to reduce the number of benzodiazepine hypnotics that were used concomitantly.

1. Introduction

Among Japanese adults, 20–25% consider themselves as having insomnia, and 4–6% habitually use sleep agents (Kim et al., 2000). In particular, the rate is higher in the elderly population (Itani et al., 2016). Benzodiazepine receptor-mediated sleep agents (BZs) have been the principal prescription drugs for insomnia for the past 50 years. BZs act on $GABA_A$ receptors to induce sleep. This not only induces sleep, but also mediates several adverse effects, including muscle relaxation, anterograde amnesia, rebound insomnia, and drug-dependence (DeVane, 2016).

Ramelteon is believed to possess a novel mechanism of action by inducing quasi-natural physiological sleep via selective binding to melatonin receptors without causing rebound or withdrawal symptoms (Asnis et al., 2016). Ramelteon is a selective melatonin MT1/MT2 receptor agonist, which is known to suppress firing of neural activities in the suprachiasmatic nucleus to induce sleep through MT1 receptors, and to shift the circadian rhythm phase of one's biological clock through MT2 receptors. Administration of ramelteon reduced sleep-onset time and increased total sleep time in adult patients with chronic insomnia (Monti et al., 2016). Moreover, ramelteon does not bind to receptors for GABA/benzodiazepines, opioids, muscarine, serotonin, or dopamine. It has a completely different mechanism of action from that of BZs. Compared to BZs, it is known to cause less frequent drug abuse, dependence, and next-day cognitive dysfunction (Asnis et al., 2016).

In Japan, in the 2012 revision of medical service fees, a policy was

Abbreviations: ANOVA, analysis of variance; BZ, benzodiazepine receptor; GAF, Global Assessment of Function; PSQI-J, Pittsburgh Sleep Quality Index, Japanese version; QOL, quality of life

* Corresponding author at: Division of Psychiatry, Department of Clinical Neuroscience, Faculty of Medicine, University of Miyazaki, 5200 Kihara, Kiyotake–cho, Miyazaki City, Miyazaki Prefecture, 889-1692, Japan.
E-mail address: keiko_naono@med.miyazaki-u.ac.jp (K. Naono-Nagatomo).

https://doi.org/10.1016/j.ajp.2018.05.016
Received 4 January 2018; Received in revised form 17 April 2018; Accepted 13 May 2018
1876-2018/ © 2018 Elsevier B.V. All rights reserved.

announced to reduce remuneration of medical services for prescription of three or more antidepressants or sleep agents, which would discourage co-prescription of several BZs (Okumura et al., 2015). Moreover, revision of the medical fees in 2012 proposed a reduction in the medical fees for cases involving a prescription of three or more anxiolytics or sleep agents, which would limit the use of multi-drug regimens of BZs in Japan. However, in general practice, patient resistance due to several reasons, including rebound insomnia and dependence, makes it difficult to reduce the dose or discontinue the use of BZs after their use has been initiated. Moreover, withdrawal symptoms and anxiety (i.e., psychological dependence) are major barriers to dose reduction or discontinuation of BZs among patients who have been using them regularly for > 10 years.

Many reports have identified the utility of ramelteon in the gradual dose reduction and eventual discontinuation of BZs for insomnia (Furuya et al., 2013). However, the use of ramelteon in patients with a long history of insomnia has not been sufficiently examined. We hypothesized that ramelteon would help to alleviate the clinical symptoms of insomnia and thereby facilitate dose reduction of BZs. Therefore, we investigated whether ramelteon could facilitate dose reduction of BZs and improve the quality of life (QOL) in patients with a long history of BZ use for insomnia. More specifically, we sought to determine whether, in a careful attempt at gradual dose reduction and eventual discontinuation of BZs, ramelteon administration in addition to BZ sleep agents could help reduce withdrawal symptoms and maintain or improve patients' QOL while maintaining their subjective satisfaction, using a survey-based study.

2. Material and methods

2.1. Study subjects and survey period

Inclusion criteria were a diagnosis of insomnia by a psychiatrist. All patients were receiving treatment at Miyazaki University Hospital or at one of the affiliated hospitals at the time of inclusion in the study. Exclusion criteria were: 1) lack of study cooperation or unreliable data and 2) lower self-report reliability (cases associated with moderate or greater degree of intellectual disability, with an IQ score of lower than 50).

The paper-based surveys were administered to patients in-person at each visit. This was a convenience sample and formal sample size analysis was not conducted. This survey-based study was an observational study; the normal course of treatment that had been conducted in the participating facilities was observed. Patients were allocated to either one of the following two groups by the decision of four attending physicians. The "ramelteon group" was defined as a group who were administered 8 mg/day of ramelteon before sleep, as per the directions of use and dose indicated on the package insert, in addition to BZ (n = 22), while the "control group" was defined as a group of patients who were continually administered only BZs (n = 20). The survey period ran from June 1, 2012, to December 31, 2013.

Written informed consent was obtained from all participants prior to the initiation of the study. All procedures were approved by the ethics committee of the University of Miyazaki.

2.2. Survey items

Study patients were administered a drug-dependence survey (Yamada et al., 1993) and the self-administered questionnaire survey created for this study, which asks about typical side effects of BZs at the start of the survey (Week 0), after Week 8, and after Week 16. The drug-dependence survey consisted of a 4-point Likert scale self-administered questionnaire form (1) (Table 1), comprising six questions concerning "drug-dependence" (scores: to a great extent = 3, fairly = 2, slightly = 1, not at all = 0) and a 2-point self-administered questionnaire form, comprising six questions concerning typical side effects of BZ (2) (Table 2). The 4-point questionnaire form (1) concerning "drug-dependence" was assessed by the sum total of the scores of the six questions. For the 2-point questionnaire form (2), the questions were of the yes/no type; thus, the number of "yes" answers were counted. For the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) (self-administered), only the question "How do you evaluate your overall sleep quality over the past month?" was excerpted to assess sleep quality at Week 0, Week 8, and Week, 16 based on a 4-point (excellent = 0, good = 1, fair = 2, poor = 3) Likert scale. The Global Assessment of Functioning (GAF) Scale (Eguchi et al., 2015), a scale for assessing psychological, social, and occupational functioning was administered by the attending physician and was used to assess changes between Week 0 and Week 16. Table 3 shows the time points for administering each survey.

2.3. Methods of analysis

All data were analyzed using two-way repeated measures analysis of variance (ANOVA), with the group (ramelteon and control groups) and the survey timing (Week 0, Week 8, and Week 16) as factors. Bonferroni correction was used for a multiple comparison when the principal effects of the group or survey timing was significant. A *t*-test was used to analyze inter-group differences in "age," "disease duration," and "number of BZs used at study initiation." The Wilcoxon rank-sum test was used to study the changes in the number of BZs used during the 16 weeks. A statistical package, SPSS Base Model 22 (IBM, Japan), was employed for statistical analysis. In all the statistical tests, the significance level was set to $p = 0.05$.

3. Results

3.1. Background of patients

Forty-two patients among those who had been receiving treatment for insomnia during the survey period consented to participate in the study. All the patients completed all the surveys and there were no incomplete or partial responses; no data in any of the surveys were missing, yielding a continuation rate of 100%. None of the patients presented poor cooperation or poor self-report reliability associated with a moderate or greater degree of intellectual disability; thus, all patients were studied. Table 4 shows the composition and Table 5 shows disease history of the ramelteon and control groups during the survey. Of the 42 study subjects, 20 subjects were male and 22 were female. Their overall average age at the start of the survey was 52.4 ± 11.7 (mean ± SD) and the overall average disease duration was 11.3 ± 9.6 years. There was no significant difference in terms of average age ($p = 0.059$) and average duration of disease ($p = 0.922$) between the two groups.

Fig. 1 shows changes in the number of BZs used from the start to the end of the 16-week survey for both the ramelteon and control groups. Among the 22 patients in the ramelteon group, six patients were able to reduce the number of BZs used, and two patients were able to discontinue BZ use. In contrast, among the 20 patients in the control group, only one patient was able to reduce the number of BZs, and none were able to discontinue BZ use. There was no significant difference between the two groups in terms of BZ use at the start of the survey. The Wilcoxon rank-sum test showed that the number of BZs used decreased significantly ($p = 0.009$) in the ramelteon group after Week 16, while no such change was observed in the control group (Fig. 1).

3.2. Self-administered questionnaire (1) and (2) and change in quality of sleep measured by PSQI-J

Table 6 shows changes in the total scores of questionnaire (1) concerning sleep drug-dependence. A two-way repeated measures ANOVA revealed no significant difference in changes in the total scores

Download English Version:

https://daneshyari.com/en/article/6787291

Download Persian Version:

https://daneshyari.com/article/6787291

Daneshyari.com