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Original Article

Association between sleep duration and hemoglobin A_{1c} level

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Abstract

Objective: The association between sleep habits and hemoglobin A_{1c} (HbA_{1c}) level has not been sufficiently examined. In the present study of residents in a local community, the associations between sleep duration and HbA_{1c} level were examined.
Methods: Self-administered questionnaires were mailed to 1062 residents in a rural community in Japan, and completed questionnaires were collected. At the time of collection, the fasting plasma glucose and HbA_{1c} levels were measured using peripheral blood samples. For the analyses, values that were considered to represent high levels were a fasting plasma glucose level of $\geqslant$126 mg/dl and a HbA_{1c} level of $\geqslant$6.5%. Logistic regression analyses were performed to examine the associations between sleep duration and high fasting plasma glucose or high HbA_{1c} levels.
Results: The prevalence of high fasting plasma glucose and high HbA_{1c} levels was significantly high ($p < 0.01$) in subjects with a short or a long sleep duration. Logistic regression analyses demonstrated a significant association between high HbA_{1c} level and sleep duration. The adjusted odds ratios for a high HbA_{1c} level showed high values with regard to both short and long sleep durations.
Conclusions: HbA_{1c} level showed a U-shaped association with sleep duration. These results suggest that there may be an appropriate range of sleep duration in individuals with glucose tolerance disorders. It is expected that the present findings will contribute to the treatment and prevention of diabetes mellitus.

Keywords: Sleep; Diabetes mellitus; Hemoglobin A_{1c}; Glucose; Epidemiology; U-shaped association

1. Introduction

According to a fact-finding survey of diabetes mellitus conducted in 2002 by the Ministry of Health, Labour and Welfare in Japan, the number of people with a hemoglobin A_{1c} (HbA_{1c}) level of $\geqslant$ 6.1% (those who were strongly suspected to have diabetes) and those currently receiving treatment for diabetes mellitus was approximately 7.4 million, and the number of people with an HbA_{1c} level of $\geqslant$5.6% but <6.1% (those in whom the possibility of diabetes could not be ruled out) was approximately 8.8 million, giving an overall total of approximately 16.2 million [1]. These figures were higher than those reported in an earlier survey conducted in 1997. Diabetic nephropathy was ranked first (41.3%) among the diseases that necessitated dialysis. In addition, diabetic retinopathy-induced visual impairment is detected in approximately 3000 people annually [1]. Therefore, diabetes mellitus is currently recognized to be an important public health issue in Japan Fig. 1.

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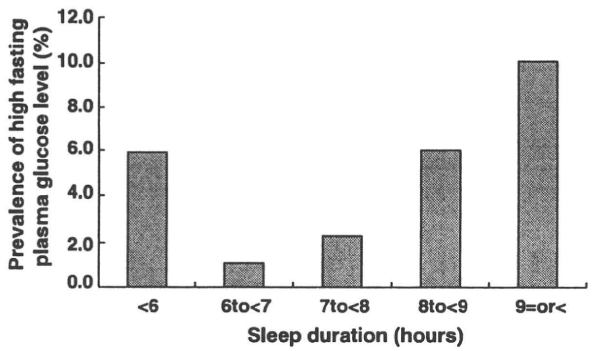

Fig. 1. (Title) Association between prevalence of high fasting plasma glucose level and sleep duration. *Note:* A U-shaped association was recognized between prevalence of high fasting plasma glucose level and sleep duration. A fasting plasma glucose level of ⩾126 mg/dl was considered to be a "high plasma glucose level."

In addition to diet, exercise habits, alcohol consumption, and smoking habits, sleep habits are considered to be a particularly important factor associated with lifestyle-related diseases, including diabetes. Moreover, changes in social habits, as exemplified by the increase in the number of shops and restaurants that stay open until late at night, coupled with the increase in the number of people who stay up until late at night browsing the Internet (an outcome of the popularization of the Internet), have resulted in a new nightlife culture in Japanese society. Hence, an increase in the prevalence of sleep disturbance has been recognized as a social problem in recent years. According to large-scale epidemiological studies on sleep in Japan, approximately one out of five Japanese adults has some type of sleep problem [2], and sleep duration among Japanese adults tends to decrease year after year [3]. For example, in the general Japanese population, the average sleep duration on weekdays was reported to have decreased by more than 30 minutes over the 35 years between 1970 and 2005 [3].

With the increase in the number of studies on sleep, it has been revealed that sleep disturbance may cause various mental and physical problems [4–7]. Various studies have reported associations between depression, a mental disease, and sleep disturbance [8,9]. Several studies have also reported that sleep disturbances such as insomnia and short sleep duration impair glucose tolerance [4,5,10]. In addition, it is known that the complication rate of depression developed by diabetic patients is high because of their fear of developing complications [11]. Other contributing factors include stressful lifestyles that involve regular insulin injections, and strict diet and exercise therapies [12,13].

For the prevention and treatment of diabetes, it is important to clarify the associations between sleep and both glucose tolerance and diabetes. In comparison with the plasma glucose level, the HbA_{1c} level shows less fluctuation and is less influenced by short-term lifestyle habits such as calorie intake. Therefore, the HbA_{1c} level is considered to be an important test parameter during the management of diabetes, a disease that has a prolonged course of development. However, to date, only a few large-scale studies have been conducted on the associations between sleep habits and HbA_{1c}. In the present study of residents in a rural community in Japan, the associations between sleep duration and fasting plasma glucose and HbA_{1c} level were examined under the situation in which depression was adjusted Fig. 2.

2. Methods

2.1. Subjects

We started a longitudinal survey in 2005 to collect and accumulate data on the lifestyle habits and health status of the residents of Iwaki-machi in order to contribute to the maintenance and promotion of their good health. To recruit the study participants, we mailed written notifications about the present longitudinal survey to residents aged 20 years or above as of March 31, 2005. Those interested in participating were requested to reply by mailing a consent letter. On the day of the survey, the survey details were verbally explained to the participants and they were instructed to sign the consent forms for participation and cooperation. At the beginning of this longitudinal survey, there were 1067 entries.

2.2. Data collection

Approval of the Ethics Committee of the institutions to which the authors belong was obtained prior to the start of the study. The first data collection was performed from April 19–28, 2005. During this period,

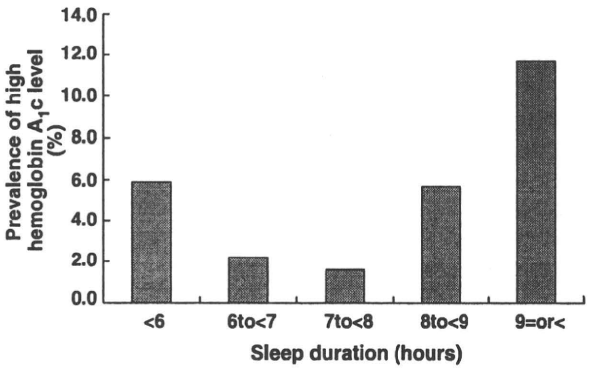

Fig. 2. (Title) Association between prevalence of high hemoglobin A_{1c} level and sleep duration. *Note:* A U-shaped association was recognized between prevalence of high hemoglobin A_{1c} level and sleep duration. A hemoglobin A_{1c} level of ⩾6.5% was considered to be a "high hemoglobin A_{1c} level."

the participants were instructed to report to the Health and Welfare Center of the municipality. A self-administered questionnaire was mailed to the participants 2–3 weeks before the day of the survey, and completed questionnaires were collected on the day of the survey. At the time of collection, we confirmed whether or not the questionnaires were complete; any participants with an incomplete questionnaire were instructed to complete the questionnaire immediately. Data on sleep habits, physical measurements (height, weight, and blood pressure), blood samples for laboratory examinations, and electrocardiogram and X-ray findings were collected.

2.3. Measures

The self-administered questionnaire consisted of queries concerning the following three items: (1) sonodemographic information, (2) sleep habits and sleep problems, and (3) the Center for Epidemiologic Studies Depression Scale (CES-D) [14].

Five questions on sleep during the past month included in this questionnaire were as follows:

(1) [Sleep duration]: "What was your actual daily sleep duration? Please also include the duration of your naps."
(2) [Difficulty initiating sleep (DIS)]: "How often did you find it difficult to fall asleep within 30 min of retiring to bed?"
(3) [Difficulty maintaining sleep (DMS)]: "How often do you find it difficult to go back to sleep after waking during the night or too early in the morning?"
(4) "How often do you have trouble staying alert when you are required to refrain from sleep (at work, etc.)?"
(5) "How often have you taken medication to induce sleep?"

The subjects were instructed to answer question (1) by entering the value of their average daily sleep duration. For questions (2)–(5), the following four options were provided: "never," "less than once per week," "once or twice per week," and "three times or more per week". The option "three times or more per week" was taken as an affirmative answer for questions (2)–(5).

The CES-D, which is a 20-item inventory designed specifically to assess symptoms of depression in the general population, was used to screen for current depressive states. The CES-D yields an item score (range: 0–3) and the sum of the 20-item scores (range: 0–60). Higher scores indicate increasing severity of symptoms of depression. Although this scale is designed to screen, but not diagnose, major depression, a score of 16 or higher is highly suggestive of symptoms of depression. Shima et al. developed the Japanese version of the CES-D, examined its reliability and validity, and recommended the cutoff point to be set at 16, as with the United States version of the CES-D [15].

Blood samples were collected when participants were in the fasting state. The plasma was separated, refrigerated, and then consigned to a laboratory for measurement of the HbA_{1C} and fasting plasma glucose levels. The fasting plasma glucose level was measured using the enzyme method, and the HbA_{1c} level was measured using the latex agglutination turbidimetric immunoassay [16,17].

2.4. Statistical analysis

Of the 1067 participants of the first survey, five were excluded from the analysis because either they did not complete the questionnaire or did not undergo determination of the HbA_{1c} level. The data for the remaining 1062 participants were analyzed statistically.

In the present study, in accordance with the diagnostic criteria of diabetes [18], a fasting plasma glucose level of $\geqslant 126$ mg/dl was considered to be a "high plasma glucose level" and a HbA_{1c} level of $\geqslant 6.5\%$ as a "high HbA_{1c} level." A HbA_{1c} value of 6.5% is the cutoff point that is often used as one of the target levels for preventing complications of diabetes, according to the diagnostic criteria for diabetes [18].

First, the mean values and standard deviations of the fasting plasma glucose and HbA_{1c} levels based on gender and age class were calculated. Second, the prevalence of high plasma glucose and high HbA_{1c} levels was calculated, and the associations of the sleep items with high plasma glucose and high HbA_{1c} levels were examined using χ^2 test. Finally, logistic regression analyses were performed to examine the associations of sleep duration with high plasma glucose and high HbA_{1c} levels. The high plasma glucose and high HbA_{1c} levels were input as response variables in Models I and II, respectively. The following parameters were input as covariates in both models: age, gender, obesity, systolic blood pressure, high-density lipoprotein level, triglyceride level, CES-D score, and answers to questions on sleep. SPSS14.0J for Windows was used for all statistical analyses.

3. Results

The distributions of the analyzed subjects based on gender and age classification are presented in Table 1. Among both men and women, participants aged 50 years and above accounted for approximately 70% of the study population.

The prevalence of high fasting plasma glucose and HbA_{1c} levels based on gender and age classification and the mean values and standard deviations of the fasting plasma glucose and HbA_{1c} levels are presented in Table 2. The prevalence of high plasma glucose and high

Table 1
The distributions of the analyzed subjects by gender and age classification

Age classification	Male *N* (%)	Female *N* (%)	Total *N* (%)
20–39	57(14.0)	86(13.1)	143(13.5)
40–49	61(15.0)	81(12.3)	142(13.4)
50–59	99(24.4)	163(24.8)	262(24.7)
60–69	94(23.2)	189(28.8)	283(26.6)
70–	95(23.4)	137(20.9)	232(21.8)
Total	406(100.0)	656(100.0)	1062(100.0)

HbA_{1c} levels was higher among men and women aged 60 years and above.

The associations of each sleep item with fasting plasma glucose and HbA_{1c} level are presented in Table 3. A significant association was demonstrated between sleep duration and the prevalence of a high plasma glucose level ($p < 0.01$). The prevalence of a high plasma glucose level was lowest for sleep durations of $\geqslant 6$ h but <7 h. The prevalence of a high plasma glucose level tended to become higher for sleep durations shorter or

Table 2
Prevalence of glucose intolerance by gender and age classification

Age classification	*N*	Prevalence of high fasting plasma glucose level (%)	95% CI	Mean ± SD	Prevalence of high HbA_{1c} level (%)	95% CI	Mean ± SD
Male							
20–39	57	1.8	0.0–5.3	79 ± 12	1.8	0.0–5.3	4.8 ± 0.5
40–49	61	3.3	0.0–7.8	84 ± 10	1.6	0.0–4.7	4.9 ± 0.4
50–59	99	6.1	1.4–10.8	93 ± 29	8.1	2.7–13.5	5.3 ± 0.9
60–69	94	9.6	3.6–15.6	96 ± 27	11.7	5.2–18.2	5.4 ± 0.9
70–	95	10.5	4.3–16.7	96 ± 21	10.5	4.3–16.7	5.4 ± 0.9
Total	406	6.9	4.4–9.4	91 ± 23	7.6	5.0–10.2	5.2 ± 0.9
Female							
20–39	86	0.0	0.0–0.0	77 ± 6	0.0	0.0–0.0	4.7 ± 0.5
40–49	81	1.2	0.0–3.6	83 ± 18	1.2	0.0–3.6	5.0 ± 0.4
50–59	163	1.2	0.0–2.9	87 ± 15	1.8	0.0–3.8	5.1 ± 0.6
60–69	189	6.3	2.8–9.8	93 ± 19	5.3	2.1–8.5	5.2 ± 0.6
70–	137	5.8	1.9–9.7	95 ± 27	5.8	1.9–9.7	5.3 ± 0.9
Total	656	3.5	2.1–4.9	88 ± 19	3.4	2.0–4.8	5.1 ± 0.7
Total	1062	4.8	3.5–6.1	89 ± 21	5.0	3.7–6.3	5.2 ± 0.7

CI, confidence interval; SD, standard deviations; HbA_{1c}, hemoglobin A_{1c}.

Table 3
Prevalence of glucose intolerance by sleep duration and sleep problems

	N	Prevalence of high fasting plasma glucose level (%)	95% CI	*P*-value	Mean ± SD	Prevalence of high HbA_{1c} level (%)	95% CI	*P*-value	Mean ± SD
Sleep duration (h)				<0.01				<0.01	
<6	51	5.9	0.0–12.4		93 ± 39	5.9	0.0–12.4		5.2 ± 1.0
6 to <7	183	1.1	0.0–2.6		85 ± 12	2.2	0.0–4.2		5.1 ± 0.5
7 to <8	308	2.3	0.6–4.0		86 ± 15	1.6	0.2–3.0		5.0 ± 0.5
8 to <9	332	6.0	3.4–8.6		91 ± 21	5.7	3.2–8.2		5.1 ± 0.8
9 = or <	188	10.1	5.8–14.4		95 ± 27	11.7	7.1–16.3		5.4 ± 1.1
Difficulty intiating sleep				0.68				0.85	
No	970	4.7	3.4–6.0		89 ± 21	5.1	3.7–6.5		5.1 ± 0.8
Yes	87	5.7	0.8–10.6		91 ± 21	4.6	0.2–9.0		5.2 ± 0.7
Difficulty maintaining sleep				0.24				0.46	
No	958	4.9	3.5–6.3		89 ± 21	5.0	3.7–6.5		5.1 ± 0.8
Yes	92	2.2	0.0–5.2		91 ± 17	3.3	0.0–7.0		5.2 ± 0.6
Use of hypnotic medication				0.75				0.02	
No	1018	4.7	0.6–8.8		89 ± 21	4.6	3.3–5.9		5.1 ± 0.7
Yes	29	3.4	0.0–10.0		92 ± 26	13.8	1.2–26.4		5.3 ± 1.0
Difficulty remaining alert				0.64				0.70	
No	1034	4.5	3.2–5.8		89 ± 20	4.8	3.5–6.1		5.1 ± 0.7
Yes	14	7.1	0.0–20.6		97 ± 60	7.1	0.0–20.6		5.3 ± 1.3

CI, confidence interval; SD, standard deviations; HbA_{1c}, hemoglobin A_{1c}. *P*-values were calculated by χ^2 test.

longer than the above-mentioned range. A significant association was also demonstrated between sleep duration and the prevalence of a high HbA_{1c}level. Similarly to a high plasma glucose level, the prevalence of a high HbA_{1c} level was lowest for sleep durations of ⩾6 h but <7 h. The prevalence tended to become higher for sleep durations that were shorter and longer than the above-mentioned range.

The results of logistic regression analyses are presented in Table 4. The adjusted odds ratio for a high plasma glucose level was significantly higher for a sleep duration of ⩾9 h than for a sleep duration of ⩾7 h but <8 h. Logistic regression analysis using high HbA_{1c} as a response variable revealed significant associations with gender, sleep duration, and triglyceride level. The adjusted odds ratio for a high HbA_{1c} level was

Table 4
The results of logistic regression analyses

	High fasting plasma glucose level			High HbA_{1c} level		
	AOR	95% CI	*P*-value	AOR	95% CI	*P*-value
Age classification			0.07			0.12
30–39	2.10	0.19–23.84		2.15	0.19–24.50	
40–49	3.85	0.46–32.46		5.07	0.62–41.69	
50–59	9.07	1.15–71.63		9.02	1.14–71.60	
60–69	8.18	1.00–66.86		6.60	0.80–54.60	
70–	1.00			1.00		
Gender			0.13			0.03
Male	1.00			1.00		
Female	0.61	0.32–1.16		0.49	0.26–0.94	
Sleep duration (h)			0.07			0.02
<6	3.60	0.79–16.41		4.96	1.03–23.96	
6 to <7	0.59	0.12–3.00		0.97	0.22–4.26	
7 to <8	1.00			1.00		
8 to <9	2.03	0.76–5.41		2.92	1.03–8.27	
9 = or <	3.16	1.14–8.75		4.96	1.70–14.50	
Systolic blood pressure			0.32			0.11
<130 mm Hg	1.00			1.00		
130 mm Hg = or <	1.41	0.72–2.8		1.75	0.89–3.45	
Body mass index			0.35			0.26
<25	1.00			1.00		
25 = or <	0.73	0.38–1.41		0.68	0.35–1.33	
High-density lipoprotein cholesterol level			0.28			0.45
<40 mg/dl	1.00			1.00		
40 mg/dl = or <	0.32	0.04–2.53		1.55	0.49–4.89	
Triglyceride level			0.39			0.05
<150 mg/dl	1.00			1.00		
150 mg/dl = or <	1.51	0.59–3.85		2.27	1.00–5.16	
Difficulty remaining alert			0.48			0.49
No	1.00			1.00		
Yes	2.27	0.42–1.62		2.22	0.23–21.17	
Difficulty intiating sleep			0.26			0.80
No	1.00			1.00		
Yes	1.90	0.62–5.78		0.85	0.25–2.91	
Difficulty maintaining sleep			0.17			0.20
No	1.00			1.00		
Yes	0.34	0.07–1.58		0.37	0.08–1.67	
Use of hypnotic medication			0.62			0.17
No	1.00			1.00		
Yes	0.57	0.06–5.15		2.71	0.66–11.13	
Going to the rest room during night			0.58			0.57
No	1.00			1.00		
Yes	0.83	0.42–1.62		0.82	0.43–1.59	
Having a pain			0.61			0.29
No	1.00			1.00		
Yes	1.31	0.46–3.76		1.70	0.63–4.57	
CES-D score			0.36			0.73
<16	1.00			1.00		
16 = or <	0.67	0.28–1.60		0.87	0.39–1.93	

CI, confidence interval; HbA_{1c}, hemoglobin A_{1c}; AOR, adjusted odds ratio; CES-D, the Center for Epidemiologic Studies Depression Scale. In each section, the missing data have been excluded from the statistical analyses.

significantly higher for sleep durations of <6 h and ⩾8 h than for a sleep duration of ⩾7 h but <8 h. Thus, a U-shaped association was recognized between high HbA_{1c} and sleep duration. No significant association was found between a high fasting plasma glucose level and the CES-D score or between a high HbA_{1c} level and the CES-D score.

4. Discussion

This is the first report to demonstrate that the adjusted odds ratio for HbA_{1c} level is significantly high for both short and long sleep durations. Previous cross-sectional studies that examined the association between diabetes mellitus and sleep showed that the prevalences of DIS, DMS, and excessive daytime sleepiness were high among diabetics [6,7]. In a prospective study of 8269 Germans, Meisinger et al. reported that DMS might be a risk factor for onset of Type 2 diabetes [19]. Similar results were reported in prospective studies conducted in other Western countries [20,21]. In Japan, Kawakami et al. followed 2649 subjects over eight years and reported that DMS and DIS might be risk factors for the onset of diabetes [22]. With regard to the association between diabetes and sleep duration, the Sleep Heart Health Study conducted in the United States with approximately 1500 subjects revealed that glucose tolerance was impaired at sleep durations of ⩽6 h or ⩾9 h [23]. In the present study, a U-shaped association was recognized between glucose tolerance and sleep duration, even when glucose tolerance was assessed using the plasma HbA_{1c} level as a measure. This result was rationally in agreement with the result of the above-mentioned study.

The association between short sleep duration and impaired glucose tolerance can be explained in terms of the functions of several hormones. It is known that insomnia stimulates the cerebral cortex, cerebral limbic system, and hypothalamus, which in turn induces the secretion of catecholamines from the sympathetic ganglion and adrenal medulla and of cortisol from the pituitary–adrenal system [4]. These hormones may function to increase the plasma glucose level. Moreover, physiological experiments have shown that the blood cortisol concentration and insulin resistance are increased when sleep is prevented [4,24,25]. Furthermore, recently, it has recently been clarified that the blood concentration of leptin, which suppresses appetite, is decreased and that the blood concentration of ghrelin, which promotes appetite, is increased when individuals are deprived of sleep [19,26]. The association between short sleep duration and impaired glucose tolerance may be explained in terms of the function of these appetite-regulating hormones. Unfortunately, since measurement of hormone concentrations was not included in the present study, any associations among short sleep duration, glucose tolerance, and hormone concentrations could not be elucidated. We intend to investigate such associations in future studies.

Although it can be reasonably argued that an association exists between short sleep duration and impaired glucose tolerance, the biological mechanisms underlying the association between long sleep duration and impaired glucose tolerance cannot be explained easily. It is known that neuropathic pain or nocturia leads to disturbed sleep [27] and increases the prevalence of insomnia symptoms such as DIS and DMS among diabetics [6,21]. It is possible that sleep duration increases to compensate for the shallow sleep caused by neuropathic pain or nocturia among diabetics. Therefore, we performed a logistic regression analysis using "having pain" and "going to the toilet during the night" as covariates. However, these two factors did not explain the association between long sleep duration and high HbA_{1c} level. A possibility that various other complications of diabetes may be associated with long sleep duration and impaired glucose tolerance, and that they act as confounding factors, cannot be refuted. Future studies on long sleep duration in the light of physiologic and epidemiologic data are expected to yield information on this issue.

Since the prevalences of depression and depressive symptoms among diabetic patients have been reported to be high [11], an association between a high HbA_{1c} level and the CES-D score was examined. However, no significant association was observed in the present study. In addition, the possibility that depression may have produced a confounding effect on the association between HbA_{1c} and sleep was considered. However, after depression was adjusted for, the significant association between sleep duration and HbA_{1c} continued to exist.

Since the latter half of the 1960s, it has been known that the mortality risk is high for individuals with both short and long sleep durations, and that there is a U-shaped association between sleep duration and mortality risk [28–31]. In recent years, U-shaped associations have been recognized between sleep duration and the morbidity risks of diabetes, obesity, hypertension, and coronary heart disease (CHD) [32–35]. It is well known that diabetes mellitus, obesity, and hypertension are morbidity risk factors for CHD. The fact that U-shaped associations exist between these pathological conditions and sleep duration may explain the U-shaped association between CHD and sleep duration, and consequently between the mortality risk of CHD and sleep duration. Diabetes mellitus, obesity, and hypertension are pathological conditions that have a tendency to develop simultaneously and affect each other. Therefore, when examining an association between one of these pathological conditions and sleep duration, it is necessary to adjust for the remaining two. In the present

study, after inputting body mass index and systolic blood pressure as covariates into the logistic regression model, the U-shaped association between sleep duration and HbA_{1c} level was confirmed. From this result, it may be inferred that neither short nor long sleep duration is favorable for glucose metabolism. We expect that our findings will be applicable to future studies, and will make a useful contribution to preventive medicine and clinical practice.

There were several limitations in the present study. First, as self-reported questionnaires were used to obtain data on sleep duration, the data were not objective. However, some studies have stated that self-reported data on sleep status are concurrent, to a certain extent, with physiological data [36,37]. Second, since this study was cross-sectional, causal relationships between glucose metabolism disorders and sleep behavior could not be established. Therefore, we were unable to infer whether short or long sleep duration induces impaired glucose tolerance and consequently diabetes mellitus, or in contrast, whether impaired glucose tolerance induces sleep disturbance. Third, since a high percentage of the study subjects were elderly, there was a selection bias. Fourth, the questionnaire used did not include all items known to affect sleep and glucose metabolism. Employment status, noise, home environment, smoking habit, and alcohol consumption may affect sleep and glucose metabolism. Future analyses should include these items as adjustment factors.

5. Conclusion

Sleep duration showed a U-shaped association with HbA_{1c} level. With regard to glucose metabolism, it is inferred that neither short nor long sleep duration is favorable, and that there may be an appropriate range of sleep duration.

Acknowledgement

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うつ病患者の不眠に対する超短時間型と長時間型ベンゾジアゼピン(BZ)系睡眠薬の有用性の検討

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はじめに

うつ病においては，睡眠障害が高い頻度で併発する。睡眠障害の中でも不眠は，患者の苦痛が大きいため，抗うつ薬と並行して睡眠薬による治療も臨床上必要となる場合が多い。睡眠薬は，血中濃度半減期の長短によって分類され，不眠の症状に応じた使い分けが推奨されている[1]。うつ病に伴う不眠では中途・早朝覚醒が特徴的で重篤度にも相関する症状と考えられている。うつ病患者の不眠，特に中途・早朝覚醒に対して睡眠薬を用いる場合は，半減期による使い分けから考えると，半減期の長い(長時間型)睡眠薬が適していることとなる。

また，気分障害(大うつ病)に対するわが国の治療アルゴリズムでは，ファーストラインの選択として，選択的セロトニン再取込阻害薬(SSRI)などの抗うつ薬による治療と並行してのベンゾジアゼピン(BZ)系薬剤の使用が認められているが，4週間以上の併用は，BZ系薬剤による副作用の危険性が有用性を上回るとして，中止することが推奨されている[2]。一般的に睡眠薬は，半減期により中止のしやすさが異なると考えられ，半減期の長い睡眠薬は短いものより中止しやすいとされる[1]。このことから，うつ病に伴う不眠にBZ系睡眠薬を用いる場合，アルゴリズムのように4週間に処方を限定すると，中止のしやすい長時間型が有利となる可能性が考えられる。

このように，うつ病に伴う不眠に対する薬物治療では，2つの面から長時間型BZ系睡眠薬が有利となる可能性が考えられるが，このことを検証した報告はない。

そこで今回，SSRIで治療を開始するうつ病患者の不眠に対して，長時間型BZ系睡眠薬であるクアゼパムおよび超短時間型BZ系睡眠薬であるトリアゾラムの有用性および不眠が改善した後の薬剤中止の容易さに関して，比較検討を行ったので報告する。

方　法

対象者は，久留米大学病院精神神経科を受診し，DSM-Ⅳ-TRにより大うつ病と診断された外来患者20名である。大うつ病の診断後，パロキセチン(10mgから開始し，40mg/日まで1週ごとに増量した後，40mg/日を維持)1回×夕食後を処方すると同時に，トリアゾラム(0.125mg/日から開始，4日後に増・減量を判断し，用量固定)か，クアゼパム(15mg/日から開始，4日後に増・減量を判断し，用量固定)のどちらかを就寝前に処方した。どちらの睡眠薬にするかは，患者の受診順に交互に割り振った。

睡眠薬を4週間処方した時点で，患者の不眠が改善しており，さらに睡眠薬の減量に対する患者の同意が得られた場合に，減量を開始した。減量に際しては，各睡眠薬の特性を考慮した減量法をそれぞれの処方患者に用いた。すなわち，超短時間型睡眠薬であるトリ

アゾラムでは，4週ごとに4分の1ずつ用量を減らし，最終的に中止した(漸減法，**図1**)。一方，長時間型睡眠薬であるクアゼパムでは，まず4分の1量ずつの漸減法を用いて半錠まで減らした後，4週ごとに服薬日の間隔を1日，2日と空けていき，最終的に中止した(漸減法＋隔日法，**図2**)。

睡眠状態については患者記入式の問診票(**表1**)および睡眠日誌を用い，うつ病の状態についてはハミルトンうつ病評価尺度(HAM-D)を用いた。両評価とも，投与前，投与開始1週後，2週後，4週後，6週後，8週後に行い，経過を追った。

薬効評価として睡眠問診点数およびHAM-Dの総得点の服薬前からの変化量を，最終評価時点である8週後，途中経過の検出である1および2週後に対して，評価した。各時点で両群間の差を検討した。それぞれの解析には，服薬前からの変化については対応あり，群間の比較については対応のないStudentのt検定をそれぞれ用い，いずれも有意水準5％未満を有意差ありと判断した。

結　果

それぞれの睡眠薬を処方した患者群の，治療開始前の背景には，いずれの項目にも両群間に差はなかった(**表2**)。

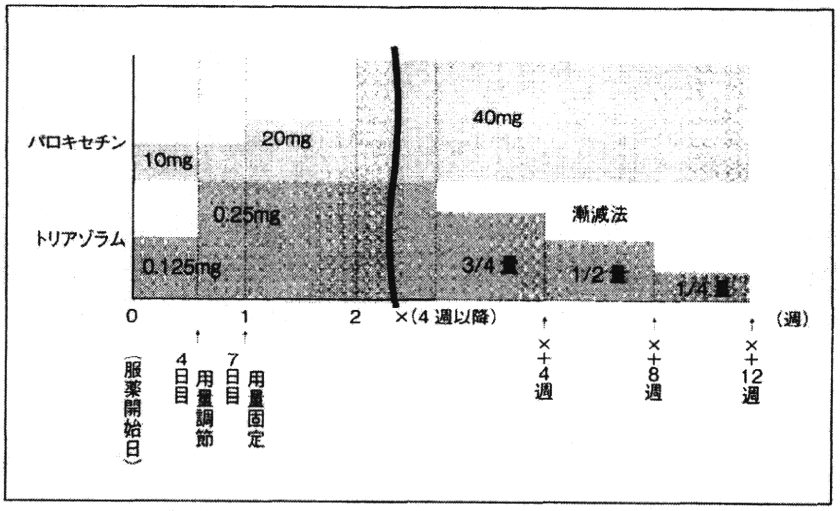

図1　超短時間型睡眠薬処方患者への処方計画

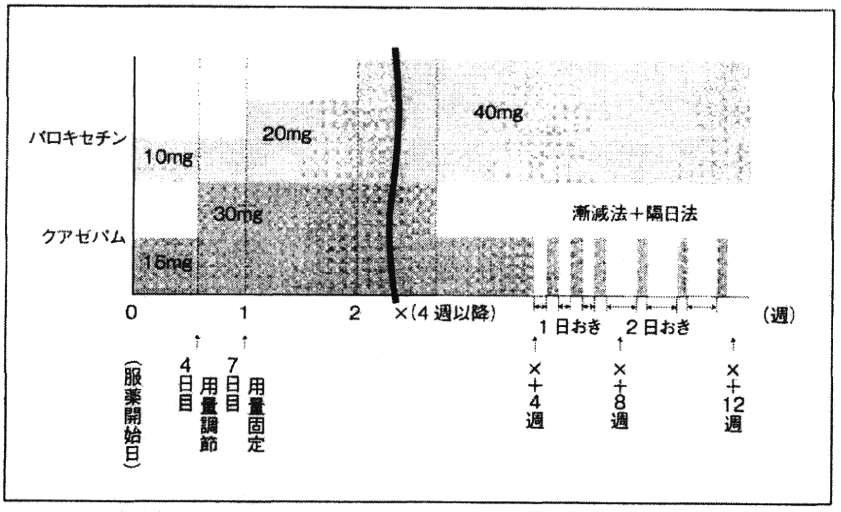

図2　長時間型睡眠薬処方患者への処方計画

表1　問診票

入眠障害	寝つき*	1. すぐ眠ってしまった（15分以内） 2. 少し時間がかかった（15～30分） 3. かなり時間がかかった（30～60分） 4. なかなか寝つけなかった（61分以上）	1 2 3 4
熟眠障害	睡眠状態*	1. ぐっすり眠れた 2. 普通に眠れた 3. あまり眠れなかった 4. ほとんど眠れなかった	1 2 3 4
	夢の回数	1. みなかった 2. みたような気がする 3. 少しみた 4. 多くみた	1 2 3 4
	夢の内容	1. 嫌な夢ではない 2. 嫌な夢だった	1 2
中途覚醒	中途覚醒の回数*	1. なし 2. 1回 3. 2～4回 4. 5回以上	1 2 3 4
	中途覚醒後の寝つきの状態	1. 起きなかった 2. すぐ眠れた 3. 少したってから眠れた 4. なかなか寝つけなかった	1 2 3 4
早朝覚醒	覚醒時刻*	1. 普通より長く眠れた 2. 普通の時間に目がさめた 3. やや早く目がさめた 4. 非常に早く目がさめた	1 2 3 4

＊睡眠状態の評価に使用した項目

表2　睡眠薬を処方した患者群の治療開始前背景

	トリアゾラム群	クアゼパム群	有意差
人数	10名（男5，女5）	10名（男5，女5）	N.S.
年齢	52.0±8.5歳	51.7±9.2歳	N.S.
HAM-D総スコア	24.5±5.6	24.0±5.4	N.S.
〈睡眠状態〉			
入眠障害	3.8±0.4	3.8±0.4	N.S.
中途覚醒	3.7±0.5	3.8±0.4	N.S.
早朝覚醒	3.9±0.3	3.9±0.3	N.S.
熟眠障害	3.7±0.5	3.8±0.4	N.S.

うつ病症状について

HAM-Dの総得点は，いずれの群も1週後から有意に減少し，8週後にはほぼ最低となった(**図3**)。2週後にはクアゼパム群がトリアゾラム群より有意に優れていた($p<0.05$)。

睡眠状態について

入眠障害は，両群とも1週後から有意な改善がみられ(トリアゾラム群およびクアゼパム群：$p<0.01$)，8週目には全例で症状が消失した。両群間の効果に差はなかった(**図4**)。熟眠障害に対しては，クアゼパム群で1週後から($p<0.05$)，トリアゾラム群で2週後から($p<0.05$)，有意な改善がみられたが，8週後でも両群のスコアはトリアゾラム群2.4±0.49，クアゼパム群2.2±0.40(平均値±SD)と，改善効果は限定的で，両群間に差はなかった(**図5**)。中途覚醒については，両薬剤とも1週後から有意な改善がみられたが(トリアゾラム群およびクアゼパム群：$p<0.01$)，1，2，8週後のすべての時点でクアゼパム群の改善がトリアゾラム群を有意に上回った(各時点とも$p<0.01$，**図6**)。早朝覚醒については，トリアゾラム群は2週後から($p<0.05$)，クアゼパム群は1週後から($p<0.01$)改善がみられ，1，2週後の効果はクアゼパム群で優れていたが(両時点とも$p<0.01$)，8週後には両群間に差はなかった(**図7**)。HAM-Dの睡眠状態に関連する3項目を別にして解析を行った結果，HAM-Dの睡眠以外の項目では両薬剤の数値に有意差がなかった(**図8**)。

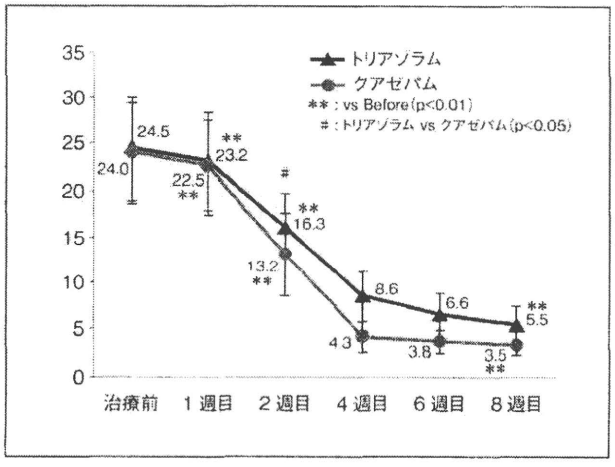

図3　HAM-D総スコア

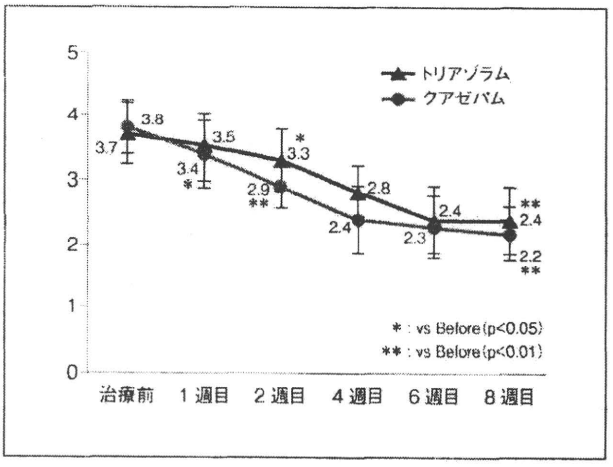

図5　熟眠障害

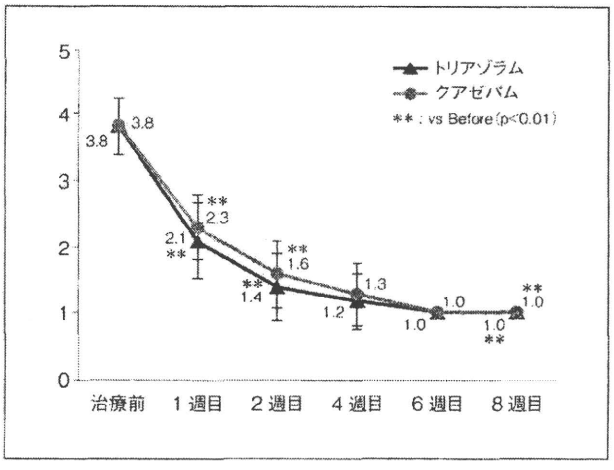

図4　入眠障害

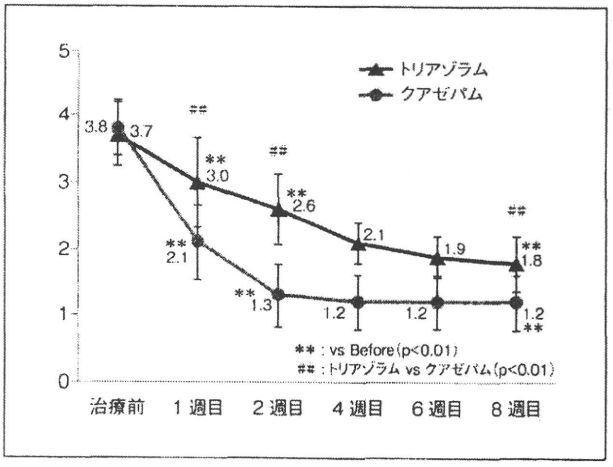

図6　中途覚醒

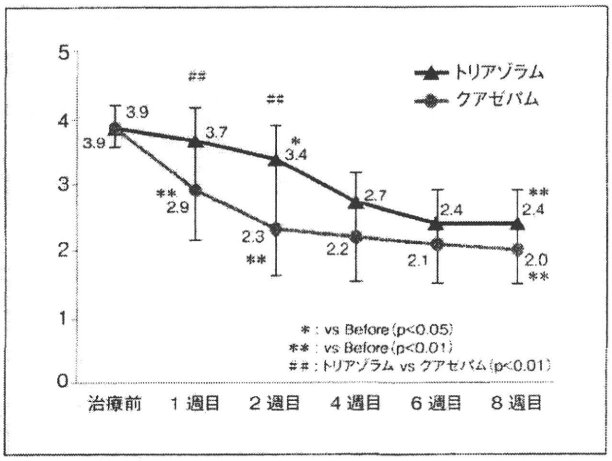

図7　早朝覚醒

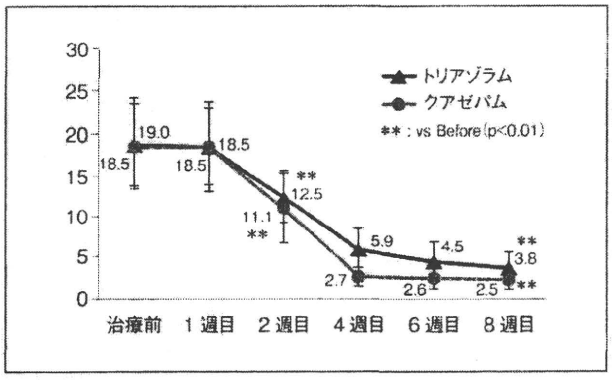

図8　HAM-D（睡眠以外）

表3　長時間型睡眠薬の離脱（漸減法＋隔日法）

症例	投与期間（週）	最高投与量（mg）	減量開始時期（週）	減量期間（週）	離脱
1	20	30	8	12	○
2	20	30	8	12	○
3	22	30	10	12	○
4	20	15	8	12	○
5	20	15	8	12	○
6	20	15	8	12	○
7	20	15	8	12	○
8	22	15	10	12	○
9	20	15	8	12	○
10	22	15	10	12	○

睡眠薬の中止について

両群の全症例で，治療開始8～12週後に不眠症状が改善・安定した（表3，4）。全症例から減量に対する同意が得られ，減量・中止を試みることができた。その結果，クアゼパム群では全10例が中止に成功した（表3）。一方，トリアゾラム群10例では中止に成功したのは4例であった。中止に失敗した6例について，クアゼパムへの置換後，同様の方法で減量・中止を試みたところ，6例中5例が中止できた（表4）。

考　察

うつ病には睡眠障害，中でも不眠が高頻度で存在し，中途・早朝覚醒が特徴的な症状である。睡眠薬はその薬物動態学的特徴，すなわち血中濃度半減期の長短によって分類され，不眠の症状に対して，入眠障害には半減期の短い睡眠薬，中途・早朝覚醒には半減期の長い睡眠薬を使用することが推奨されている[1]。このことから，うつ病で見られる中途・早朝覚醒の治療にも，半減期の長い睡眠薬がより効果的である可能性が推定されるが，現在までにその検証は行われていない。

うつ病に伴う不眠では，不眠治療だけでなく，原疾患であるうつ病の治療を行うことが必須である[3]。一

表4　超短時間型睡眠薬の離脱（漸減法）

症例	投与期間（週）	最高投与量（mg）	減量開始時期（週）	減量期間（週）	離脱	クアゼパムへの置換後の離脱
1	20	0.25	8	12	×（0.125）	○
2	20	0.25	8	12	×（0.125）	○
3	24	0.125	12	12	×（0.125）	×
4	22	0.125	10	12	×（0.125）	○
5	20	0.125	8	12	○	—
6	20	0.125	8	12	○	—
7	22	0.125	10	12	○	—
8	20	0.25	8	12	×（0.125）	○
9	24	0.25	12	12	×（0.125）	○
10	20	0.125	8	12	○	—

＊離脱の項の数値はクアゼパム置換時のトリアゾラム投与量（mg）

般に，抗うつ薬の効果発現には1－2週間必要であることから，対症療法ではあるものの，うつ病の治療初期の治療継続性を高めるために，BZ系薬剤の併用が有用とされている[2]。一方で「うつ病が改善すれば，不眠も改善するため，特に睡眠薬を処方する必要はない」とする考えがあるが，うつ病の治療によってうつ病の症状が改善した後に必ずしも不眠は改善しない。抑うつ症状が改善した後まで不眠症状が残る症例は臨床でしばしば経験するところである。最近では不眠を含む残遺症状がうつ病の再燃リスクとなることも報告されている[4]。これらのことから，うつ病患者に不眠が見られる場合，抗うつ薬による治療と並行して，BZ系睡眠薬による治療を行うことは，今日でも有用と考えてよいであろう。

今回我々は，うつ病に伴う不眠に対して，抗うつ薬パロキセチンの処方開始時に，超短時間型睡眠薬であるトリアゾラムと長時間型睡眠薬であるクアゼパムを併用し，不眠に対する有効性，抗うつ効果に及ぼす影響，ならびに不眠が改善した後の中止の容易さについて比較検討した。

両睡眠薬の半減期の違いから，血中濃度が定常状態になり効果が最大になると予測されるまでの期間が異なり，効果発現の早さにも違いが出る可能性が予想された。そこで，今回の検討では，両睡眠薬の不眠に対する有効性および抗うつ効果に及ぼす影響の評価について，通常の最終効果判定に加え，両剤の血中濃度が定常状態になる時期で効果の比較を行った。具体的には，統一プロトコルによる最終効果判定の8週後に加え，超短時間型トリアゾラムの血中濃度が定常状態になると予想される1週後，長時間型クアゼパムの血中濃度が定常状態になる2週後に，薬剤間で比較検討を行うこととした。

その結果，睡眠状態に関しては，入眠障害，熟眠障害に対しては薬剤間の効果に明らかな差は認められなかった一方で，中途覚醒，早朝覚醒については薬剤間の効果に有意な差がみられた。すなわち，中途覚醒については1，2，8週後の時点で，早朝覚醒については1，2週後の時点でクアゼパム群の効果がトリアゾラム群より上回った。

本研究では例数が両群各10例と不十分で，睡眠状態の評価に睡眠時脳波測定（PSG）やアクチグラムによる活動度測定などの客観的方法を用いていない点などに問題はあるものの，両薬の睡眠に対する効果の違いが正しいとすれば，従来言われている不眠の症状別に半減期の長短を対応させた睡眠薬を選択するのが合理的，つまり中途・早朝覚醒には半減期の長い睡眠薬がより適することが，うつ病に伴う不眠に対してあてはまることを初めて示唆したデータといえるであろう。

うつ病症状に対しては，両群ともに8週後にHAM-D総得点がほぼ最低まで改善した。うつ病に伴う不眠治療薬としての両薬剤は，半減期の長短に関わらずパロキセチンの抗うつ効果に悪影響を及ぼさないことが確認され，抗うつ薬の治療初期にBZ系薬剤の併用が有益なことを示唆した結果といえよう。

ただ，うつ病患者にとっては，十分な治療期間後にどこまで改善するかという点に加え，治療開始からどれだけ早く治療効果が現れ，苦しい症状から逃れられるかという点がQOLの改善だけでなく治療アドヒアランスの観点からも重要となる。そこで，うつ病症状の経過についてHAM-D総得点の推移をみてみると，両薬剤で違いが見られた。すなわち，2週後にクアゼパム群におけるHAM-D総得点はトリアゾラム群のそれを有意に下回っていたことから，パロキセチンにクアゼパムを併用した場合，トリアゾラムの併用よりもパロキセチンの抗うつ効果の発現が早くなる可能性が示唆された（図3）。つまり，両薬剤は同じBZ系睡眠薬ではあるが，抗うつ薬に併用した場合にその抗うつ効果の立ち上がりに違いが生じる可能性を示したものと考えられる。抗うつ薬に睡眠薬を併用することで抗うつ薬の効果が増強されることは大うつ病や全般性不安障害で報告されているが[5][6]，併用する睡眠薬の違いで，抗うつ薬の効果発現に差が出る可能性は，恐らく本研究が初めて示した。

HAM-Dの評価項目の中には睡眠状態を評価する項目があるために，この部分を除外して解析を行った。その結果，HAM-Dの睡眠状態以外の項目では両薬剤の数値に有意差はなかった。このことは，両睡眠薬の特性の違いがもたらす不眠改善効果の違いが，抗うつ薬の抗うつ効果として評価される全体像への影響が大きいことを意味すると考えられる。睡眠状態以外の抗うつ効果については，超短時間型の睡眠薬と抗うつ薬との併用でプラセボと比較して有意な改善が報告されているが[5]，今回の検討では，睡眠薬の特性が異なっても実薬同士の比較だったため，効果に差が出なかっ

た可能性が考えられる。

また，SSRIはうつ病の薬物治療において第一選択に位置づけられているが，深睡眠を減らし睡眠効率を悪化させることが多い[7]。今回の検討から，SSRIにBZ系睡眠薬を併用することで睡眠状態が改善し，SSRIの欠点をBZ系睡眠薬が補ってうつ病の治療効果を増す可能性，さらに中途・早朝覚醒に好適とされる長時間型の睡眠薬がより抗うつ薬の効果発現を早くする可能性が示唆された。

また，BZ系薬剤は依存性のために漫然と長期投与すべきではないとされる。睡眠薬による治療を考慮する場合，症状の改善後に中止することを考えれば，長時間型の睡眠薬がより中止が容易と考えられる[1]。また，気分障害の治療ガイドラインにおいてBZ系薬剤の抗うつ薬との併用は4週までとされており，それ以上は有効性が副作用のリスクを上回らないとされる[2]。ところが，従来うつ病に伴う不眠の治療において，その有効性とともに中止の容易さについて検討した検討はされていない。今回，我々はうつ病の不眠治療において，半減期の異なる睡眠薬で中止の容易さが異なるか否かについての検討も行った。

その結果，睡眠薬の中止の容易さについては，長時間型のクアゼパムでは漸減法に引き続く隔日法にて全例が中止可能であったが，超短時間型のトリアゾラムでは原則どおりの漸減法によっても中止できたのは半分以下であった。このことは従来から言われている，半減期の長い睡眠薬の方が中止が容易であること，また短時間型を中止する場合に長時間型に切り替えること（ブリッジング法）によって中止しやすくなること，を裏付けたデータといえる。

我々は以前，精神科医でも睡眠薬を中止する場合に半減期の長いものから減量・中止していく場合が多いことを報告した[8]。今回の結果は，半減期の短い睡眠薬が中止しにくいことを示唆していることから，複数の睡眠薬を減量・中止する際には，半減期の短いものから行い，長いものを残した方が中止しやすいことを裏付けると考えられる。

抗うつ効果の発現，および離脱の容易さにおける両薬の今回見られたような違いには，半減期の長短以外に，受容体選択性の違いが関与している可能性がある。トリアゾラムはBZ受容体のサブタイプに選択性がないが，クアゼパムはBZ_1（ω_1）受容体に選択的な親和性がある。BZ受容体のサブタイプではBZ_2が抗不安作用に，BZ_1が催眠作用に関与するとされる[9]ことから，BZ_1選択的なクアゼパムは抗不安作用が弱く，そのために，薬物に対する精神的依存に繋がりにくかった可能性が考えられる。BZ受容体サブタイプに対する選択性が抗うつ効果や薬剤中止の容易さの違いに結びつくかどうかについては，今後さらに例数を加えた，コントロール試験により検討する必要がある。

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