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# THE EFFECTS OF TRIAZOLAM AND RILMAZAFONE ON THE PHYSICAL AND COGNITIVE FUNCTIONS IN HEALTHY ELDERLY PERSONS

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**Abstract**
The purpose of this study is to investigate whether often used hypnotics are safe or not to elderly people by evaluating the early morning effects and residual effects on the physical and cognitive functions after hypnotic administration.
Fourteen healthy elders (3 male, 11 female ; mean age 64 years) took part in the study. Triazolam 0.125 mg, rilmazafone hydrochloride 1 mg or placebo was orally given to each subject before going to bed (11 pm). Objective evaluations including 1. Total Sway Path test (opened and closed eye) 2. Functional Reach test 3. Timed Up and Go test 4. Simply Discriminatory Reaction test 5. Critical Flicker Fusion test 6. Short-Term Memory test were done at 10 pm (an hour before subjects went to bed), 4 am, 6 am, 10 am and 2 pm.
Among all evaluations for the physical and cognitive functions, main effects between medicines were only seen in the Total Sway Path test, which is the indicator for static balance ability. When eyes were opened, trembling was significantly small in the rilmazafon group compared to the placebo group ($p=0.04$).
In this study, the hypnotics did not affect physical and cognitive functions for healthy elders. Further studies using an interdisciplinary approach with different professionals such nurses, physical therapists, pharmacists and physicians are needed for evaluating the safety use of hypnotics in the elderly patients with insomnia.

**Key words** : hypnotics, physical and cognitive functions, elders,

## Background

Bone fractures which are caused from accidental falls of the aged not only has a negative effect on their QOL, but is also a major source of medical expenses in Japan. It was reported that Japan's insomnia incidence rate of the aged is 17-21% and that 4-5% of the aged are taking hypnotic agents[1)]. Moreover, the use of hypnotics is said to be the cause of many of the bone fractures caused by falls in the aged. However, there have been other reports indicating that the insomnia itself is more related to these accidents than the use of hypnotics[2-7)].

The hypnotic agents that are frequently used to treat insomnia should not disturb movement functions[8,9)]. However, they do exert some physical effects. Therefore, when elderly people are taking these agents, a better understanding of their extent of physical impairment would help to prevent the incidence of falls associated

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with these agents[8,9].

Prior to the present study, we examined the effects of hypnotics on healthy adults with regard to their physical and cognitive functions[10,11]. None of the functions were significantly changed in healthy adults.

Although there have been some reports of causal relationships between hypnotic agents and falls in aged patients, the studies which have examined the physical and cognitive functions of the elderly people who have taken hypnotics have been limited[8,9,12,13].

Allain examined the postural trembling and cognitive function of elderly patients after a single dose of sleep-inducing medicines (zolpidem, zopiclone, lormetazepam and placebo) was taken[12]. They reported that the half-life of the hypnotic agent greatly influenced the trembling.

There have been many reports that elderly people often fall during the night and in the early morning when they wake up to go to the bathroom[2-8].

The purpose of the present study was to investigate whether often used hypnotics are safe or not for elderly people by evaluating the early morning effects and residual effects on the physical and cognitive functions after hypnotic administration.

## Methods

Fourteen healthy older subjects (3 male, 11 female ; mean age 64 years) took part in this study. The subjects underwent a medical examination before the study. They were not taking any prescribed psychotropic agents such as hypnotics or antidepressants, and did not have any serious diseases. We also ensured that they did not have an alcohol dependency or smoke more than 10 cigarettes per day. They were told to refrain from consuming alcohol, caffeine and any other medicine on the day the study was carried out and the following day.

To investigate the subjects' physical and cognitive functions the day after administration of hypnotics, the study followed a cross-over, double-blind design. Triazolam at 0.125 mg, rilmazafone hydrochloride at 1 mg, or a placebo was given to each subject to take orally before they went to bed (11 pm). These two hypnotics are often used for elder patients with insomnia in Japan[4-6].

Objective evaluations were performed at 10 pm (an hour before subjects went to bed), 4 am, 6 am, 10 am and 2 pm. Our study consisted of 3 sessions (2 consecutive days per session) of testing. The interval between each session was one week to allow for a wash-out of the drugs. The subjects went about their ordinary routines during those intervals.

The physiological (1-3) and cognitive (4-6) evaluations included 1. Total Sway Path test (opened and closed eye), 2. Functional Reach test (FRT), 3. Timed Up and Go test (TUG), 4. Simply Discriminatory Reaction test (SDR), 5. Critical Flicker Fusion test (CFF), and 6. the Short-Term Memory test (STM) as were described previously[10,11,13,14]. In brief, (1) Total Sway Path test is the indicator of the maintenance of static balance[13,14]. (2) FRT is a single item test developed as a quick screen for kinetic balance problems in older adults[13,14]. (3) TUG is presented as a basic test for functional mobility[13,14]. The test measures speed during several functional manoeuvres, which include standing up, walking, turning and sitting down. (4) SDR is a performance test program (Human Response Checker), a software by Noru-Pro Light systemsTM. The test measured the reaction time and the eye-hand coordination skill of the subjects. Subjects were required immediately to right click when a blue circle was lighted and to left click when a white circle was lighted[10,11]. (5) CFF is conducted by binocular determination of critical flicker fusion frequency. Subjects were required to discriminate flicker from fusion while the frequency of a flickering light alternately increased or decreased by 1 Hz. Threshold frequency was taken as the mean of three ascending and three descending scales[10,11]. (6) STM : A system for temporarily storing and managing information required to carry out complex cognitive tasks such as learning, reasoning, and comprehension[10,11].

The study was approved by the Akita University ethics committee and all patients gave informed written consent prior to the study. In our statistical analysis, we performed an analysis of covariance, using the treatment and time as factors. The covariance was compared to the data obtained at 10 pm (an hour before subjects took the hypnotic agent or placebo). After checking for alternate effects, we performed a multiplex comparison using the

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Bonferroni post-hoc test to determine the significance of the differences in the effects of the treatments. The significance level was $p<0.05$.

## Results

During our study, no subjects experiences any serious side effects, as determined by physical observations and vital sign checks performed before and after the hypnotic agents were taken. Furthermore, safety management was ensured by having a physician on standby.

### 1. Evaluation of Physical Functions (Table 1)

In the stabilograph test (Total Sway Path test), significant differences in the effects between medicines were seen both when patients had their eyes open and when their eyes were closed ($p=0.022$, $p=0.023$, respectively). When their eyes were open, trembling was signifi-

Table 1. Evalution of Physical Functions

| | | Total Sway Path Test | | Functional Reach Test (FRT) | Timed Up and Go Test (TUG) |
|---|---|---|---|---|---|
| | | Open eye (cm) | Close eye (cm) | cm | min |
| placebo | (Mean±SE) | 149.1± 9.9 | 181.1±13.1 | 288.6±14.3 | 7.73±0.27 |
| triazolam | (Mean±SE) | 151.9±11.6 * | 177.8±12.5 | 295.5±10.6 | 7.78±0.28 |
| rilmazafone | (Mean±SE) | 137.3± 7.5 | 161.6± 7.6 | 305.6±13.6 | 7.71±0.25 |
| main effect | | 0.022 | 0.023 | ns | ns |
| | | Fig. 1 | Fig. 2 | Fig. 3 | Fig. 4 |

Post-hoc test : Bonferroni
*$p<0.05$

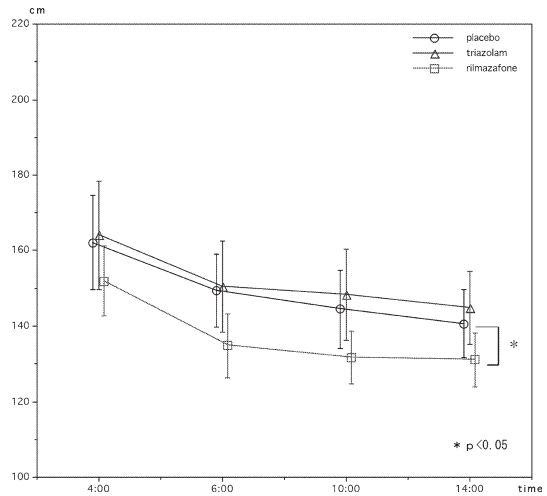


Fig. 1. The results of Total Sway Path Test (eyes open)
In the stabilograph test when patients had their eyes open, significant differences between the agents were noted ($p=0.022$). Trembling was significantly less common in the rilmazafone group compared to the placebo group ($p=0.046$).

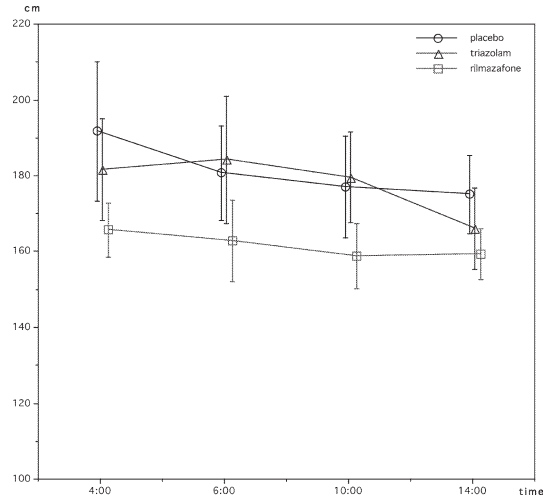


Fig. 2. The results of Total Sway Path Test (eyes closed)
When the patients' eyes were closed, significantly different effects between the treatments were seen ($p=0.023$). However no significant difference was seen between the rilmazafone group and the placebo group ($p=0.073$).

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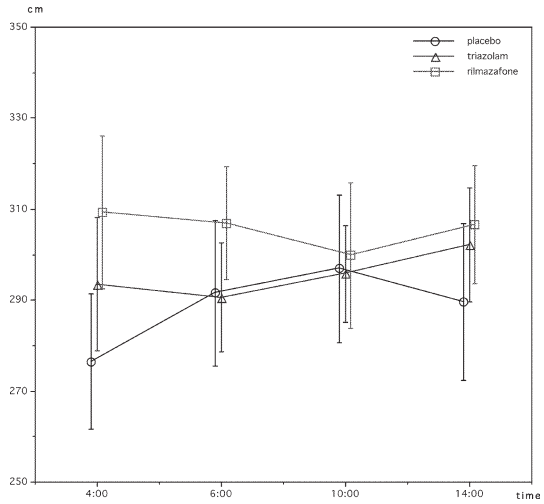


Fig. 3. The outcomes of Functional Reach Test (FRT)
In FRT, no significant differences were seen between the three groups.

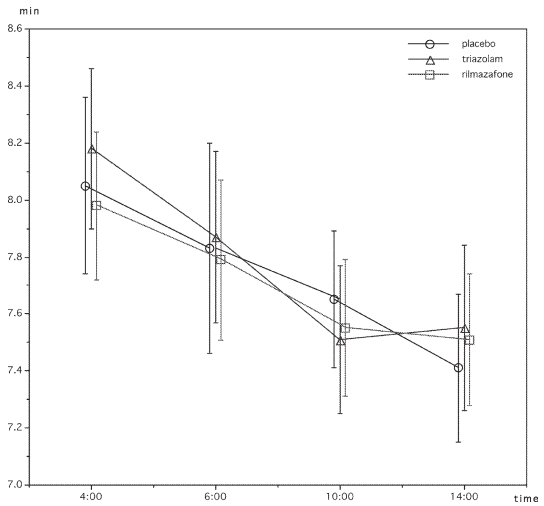


Fig. 4. The results of Timed Up and Go Test (TUG)
In TUG, no significant differences were seen between the three groups.

Table 2. Evalution of Cognitive Functions

| | | Simply Discriminatory Reaction Test (SDR) | | Critical Flicker Fusion Test (CFF) | Short-Term Memory Test (STM) |
|---|---|---|---|---|---|
| | | Rate of correction (%) | Reaction time (sec) | Hz | Rate of correction (%) |
| placebo | (Mean±SE) | 92.7±1.6 | 0.51±0.01 | 32.4±0.54 | 32.2±5.2 |
| triazolam | (Mean±SE) | 95.6±0.9 | 0.51±0.02 | 33.0±0.60 | 37.9±5.8 |
| rilmazafone | (Mean±SE) | 95.4±1.1 | 0.53±0.02 | 32.7±0.64 | 36.3±5.5 |
| main effect | | 0.031 | 0.043 | ns | ns |
| | | Fig. 5 | Fig. 6 | Fig. 7 | Fig. 8 |

Post-hoc test : Bonferroni

cantly less common in the rilmazafone group (137.3+/–7.5) compared to the placebo group (149.1+/–9.9) ($p$=0.04) (Fig. 1). However, when the subjects had their eyes closed, no significant difference was seen between the rilmazafone group (161.6+/–7.6) and the placebo group (181.1+/–13.1) ($p$=0.073) (Fig. 2).

In FRT and TUG, no significant differences were seen between the three groups (Figs. 3 and 4).

### 2. Evaluation of Cognitive Functions (Table 2)

In SDR, significantly different effects between medicines were seen with regard to the percentage of correct answers ($p$=0.031). However, there were no significant differences between the triazolam group (95.6+/–0.9) and the placebo group (92.7+/–1.6) ($p$=0.079) nor between the rilmazafone group (95.4+/–1.1) and the placebo group ($p$=0.168) (Fig. 5).

Significant differences were also seen for the different treatments in the reaction times ($p$=0.043). However, no significant differences were seen between the triazolam group (0.51+/–0.02) and the placebo group (0.51+/–0.01) ($p$=0.103) nor the rilmazafone group (0.53+/–0.02) and the placebo group ($p$=0.152) (Fig. 6). No significant differences were seen in CFF (Fig. 7) and STM (Fig. 8) between the different groups.

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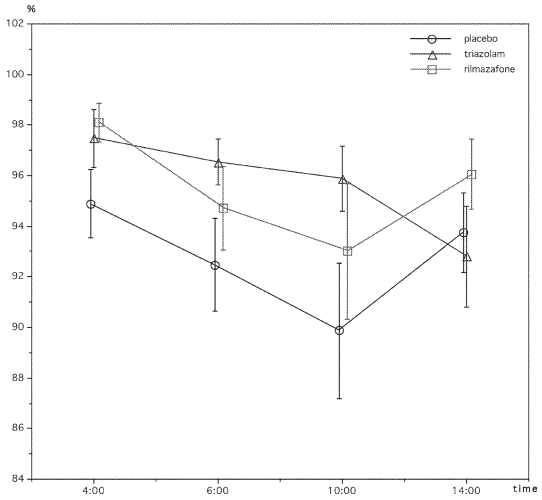


Fig. 5. The rate of correction in Simply Discriminatory Reaction Test (SDR)
For SDR, significantly different effects were seen in the percentage of correct answers for the different groups ($p=0.031$). However, no significant differences were seen between the triazolam group and the placebo group ($p=0.079$) nor between the rilmazafone group and the placebo group ($p=0.168$)

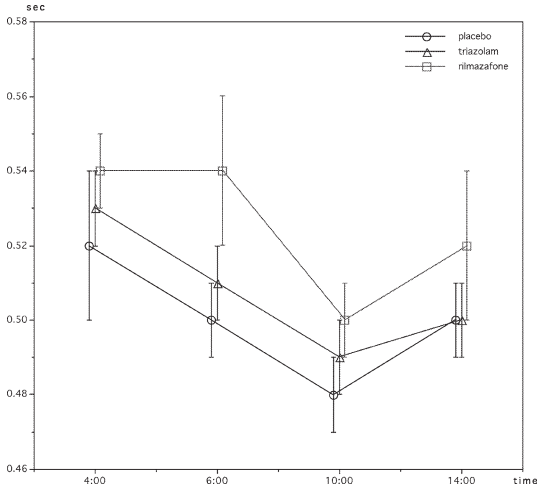


Fig. 6. The patient reaction times in Simply Discriminatory Reaction Test (SDR)
During SDR, significantly different effects between medicines were also seen in the reaction time ($p=0.043$). However, no significant differences were seen between the triazolam group and the placebo group ($p=0.103$) nor between the rilmazafone group and the placebo group ($p=0.152$).

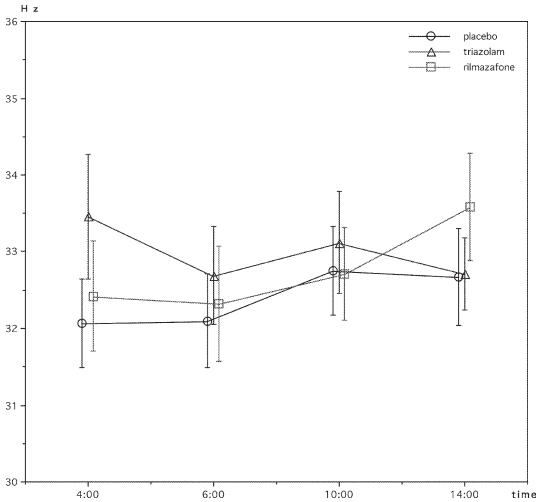


Fig. 7. The results of Critical Flicker Fusion Test (CFF)
No significant differences between treatments were seen in CFF.

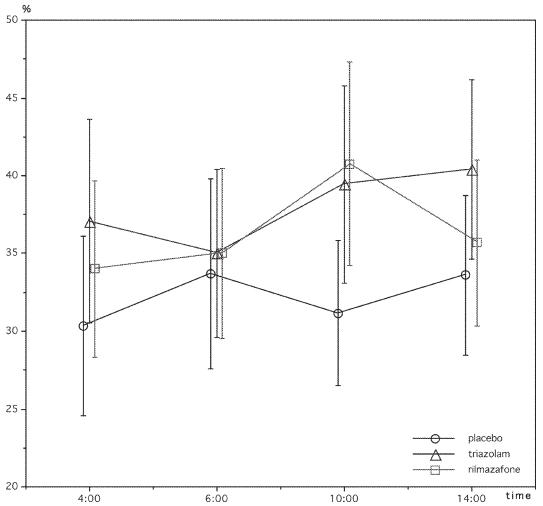


Fig. 8. The rate of correction in Short-Term Memory Test (STM)
No significant differences between treatments were seen for the rate of correction in ST.

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## Discussion

It has been reported that elderly people frequently fall when going to bathroom in the early mornings[2-5]. When going to the bathroom, many physical functions and situational assessments are needed, such as waking up, standing up from the bed, changing directions and walking[6-8]. Especially for elderly patients who take hypnotic agents, it is thought that the maintenance of static and kinetic balance, decreased muscular strength and cognitive function affect the risk of falling[9,13].

In this study, of all the physical functions evaluated, significantly different effects between agents (rilmazafone vs placebo), were only seen in the Total Sway Path test which is the indicator of static balancing ability[14]. The season why the rilmazafone show better results is unknown. No significant differences between medicines were seen in the indicators of kinetic balancing ability (FRT, TUG). This is thought to be due to the fact that, although static balance is directly affected by hypnotics, kinetic balance is more affected by the initial physical abilities of the individual subjects.

In the evaluation of cognitive function, significantly different effects between treatments were seen in SDR ($p=0.031$). Although triazolam showed a better percentage of correct answers compared with the placebo ($p=0.079$), no significant differences were seen between the other treatments. No significant differences between the agents were seen for the other indicators (CFF and STM). Although the hypnotic agents decreased CFF within several hours after their oral administration[15,16], in the current study, we did not observe any effects on CFF. Together with the results of STM, these hypnotic agents did not appear to have any significant effects on the cognitive functions of the subjects.

It is important to evaluate the conditions when elderly subjects wake up and go to the bathroom during a night for preventing accidental falls[2-5]. Especially for elderly people who take hypnotics, it is thought that the maintenance of static and kinetic balance, lower muscular strength and cognitive function affect the risk of falling[9,13]. However, it was also reported that insomnia itself was correlated with the risk of falling, rather than the effects of hypnotics[17]. In our current study, the hypnotic agents did not significantly affect the physical and cognitive functions of healthy elderly subjects. Further studies are needed to evaluate the safety of hypnotics in patients with insomnia.

On the other hand, the cultivation of risk management strategies for medical staff members are also needed to evaluate the circumstances associated with falls[18]. Using an interdisciplinary approach with different professionals such as nurses, physical therapists, pharmacists and physicians is necessary.

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