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Effects of quazepam as a preoperative night hypnotic: comparison with brotizolam

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Abstract
Purpose. The purpose of this study was to evaluate the effects of quazepam, a long-acting hypnotic, as a preoperative night medication in comparison with brotizolam, a short-acting hypnotic.
Methods. Two hundred patients (aged 30 to 70 years) admitted for elective general anesthesia at various hospitals were enrolled. Quazepam 15 mg, 30 mg, or 45 mg, or brotizolam 0.25 mg (40 patients each), was administered orally at 9 p.m. in the evening of the day before surgery. The control group (40 patients) did not receive any drugs. The quality of night sleep between the night during hospitalization and the night before surgery was compared by using a questionnaire. In the first 8 patients who received quazepam 15 mg, 30 mg, and 45 mg, the plasma concentrations of quazepam and its metabolites were measured 12 h after the drug administration, when the patients were brought into the operating room.
Results. In all the drug-administered groups, the speed of falling asleep, sleeping state, and feeling of freshness in the morning improved compared to the previous night and compared to the control group; the frequency of nocturnal awakening and dreaming decreased, and the total duration of sleep the night before surgery increased. Total duration of sleep was significantly longer in the groups with quazepam 30 mg and 45 mg than in the control and brotizolam 0.25 mg groups. No patients were drowsy with plasma concentrations of quazepam of 30 to 65 ng·ml^{-1}.
Conclusion. The preoperative night hypnotics, quazepam and brotizolam improved sleep before surgery. As a preoperative night hypnotic, quazepam 30 mg and 45 mg increased the total duration of sleep compared to brotizolam 0.25 mg.

Key words Night sleep · Preoperative · Hypnotic · Quazepam · Brotizolam

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Introduction

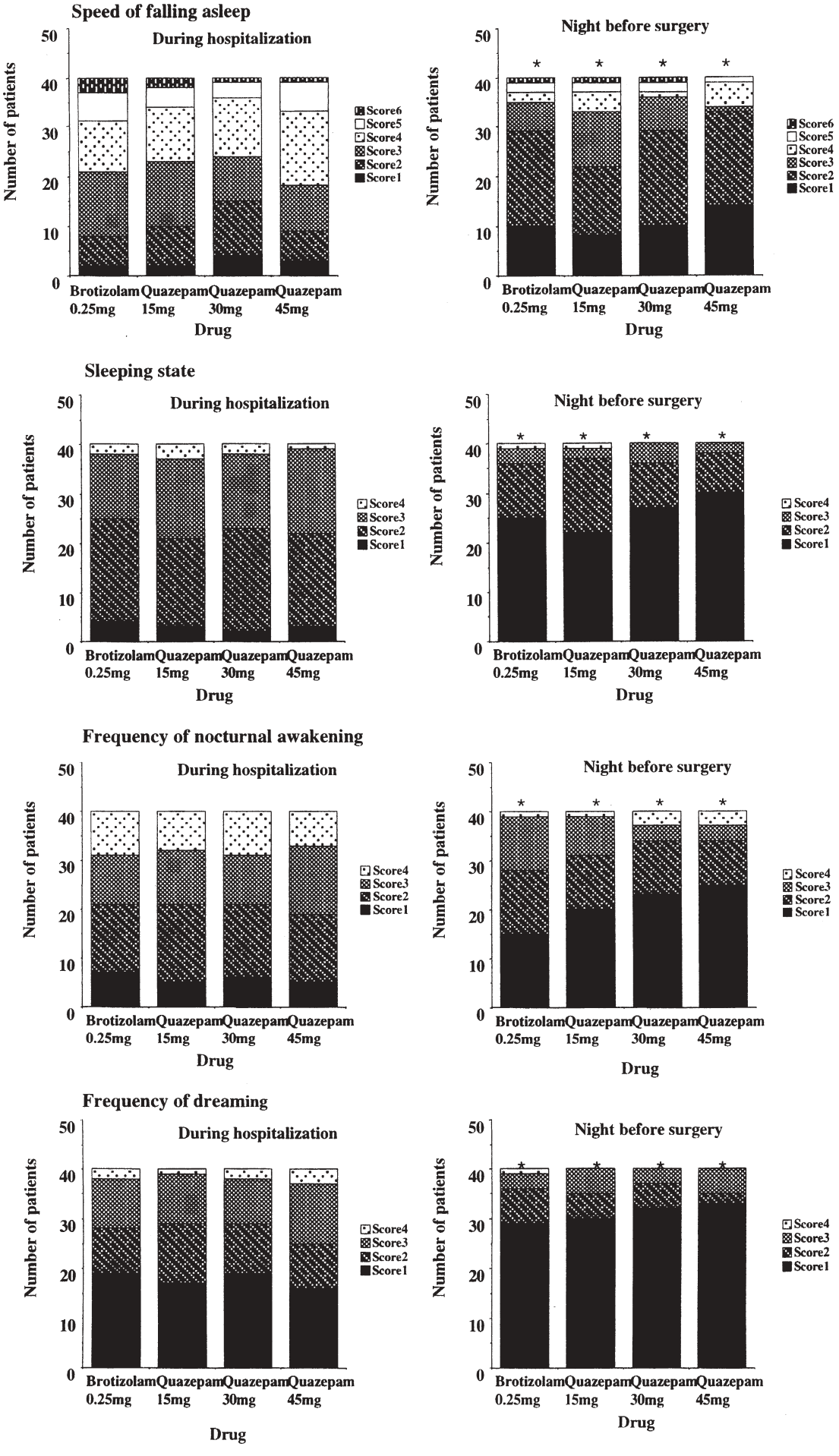
Many studies have investigated the usefulness of anesthesia premedication [1,2]. However, few studies are seen on the effects of preoperative night medication [3]. Patients scheduled for surgery usually cannot sleep well on the day before surgery because of anxiety. Therefore, they often request some hypnotics. Brotizolam, a short-acting hypnotic, at doses of 0.25 mg to 0.5 mg, was recommended as a preoperative hypnotic in a study that compared it with placebo and flunitrazepam 2 mg [3]. Quazepam in contrast, is a long-acting hypnotic developed in an effort to separate hypnotic activity from unwanted side effects, such as lack of motor coordination, and daytime sedation [4]. In the present study, we evaluated quazepam as a preoperative night hypnotic, using a questionnaire, in comparison with brotizolam, which is most frequently used in our hospitals.

Patients, materials, and methods

After obtaining the approval of the hospitals involved in the study and obtaining informed consent from the patients, 200 patients (aged 30 to 70 years), who had been admitted to hospital 2 days before elective surgery, were randomized into five groups, by a random number table. Patients suffering from liver or renal disease, drug or alcohol abuse, or chronic insomnia, and patients recently given psychoactive medication were excluded, as were pregnant women.

Quazepam 15 mg, 30 mg, or 45 mg, or brotizolam 0.25 mg (40 patients each) was administered orally at the bedside at 9 p.m. in the evening on the day before the surgery. No drugs were administered to the control group (40 patients). No coffee or tea was served in the evening that the medication was taken.

The effect was evaluated by questionnaire (see Appendix). During hospitalization, the questionnaire



(**Fig. 1.** *Continues*)

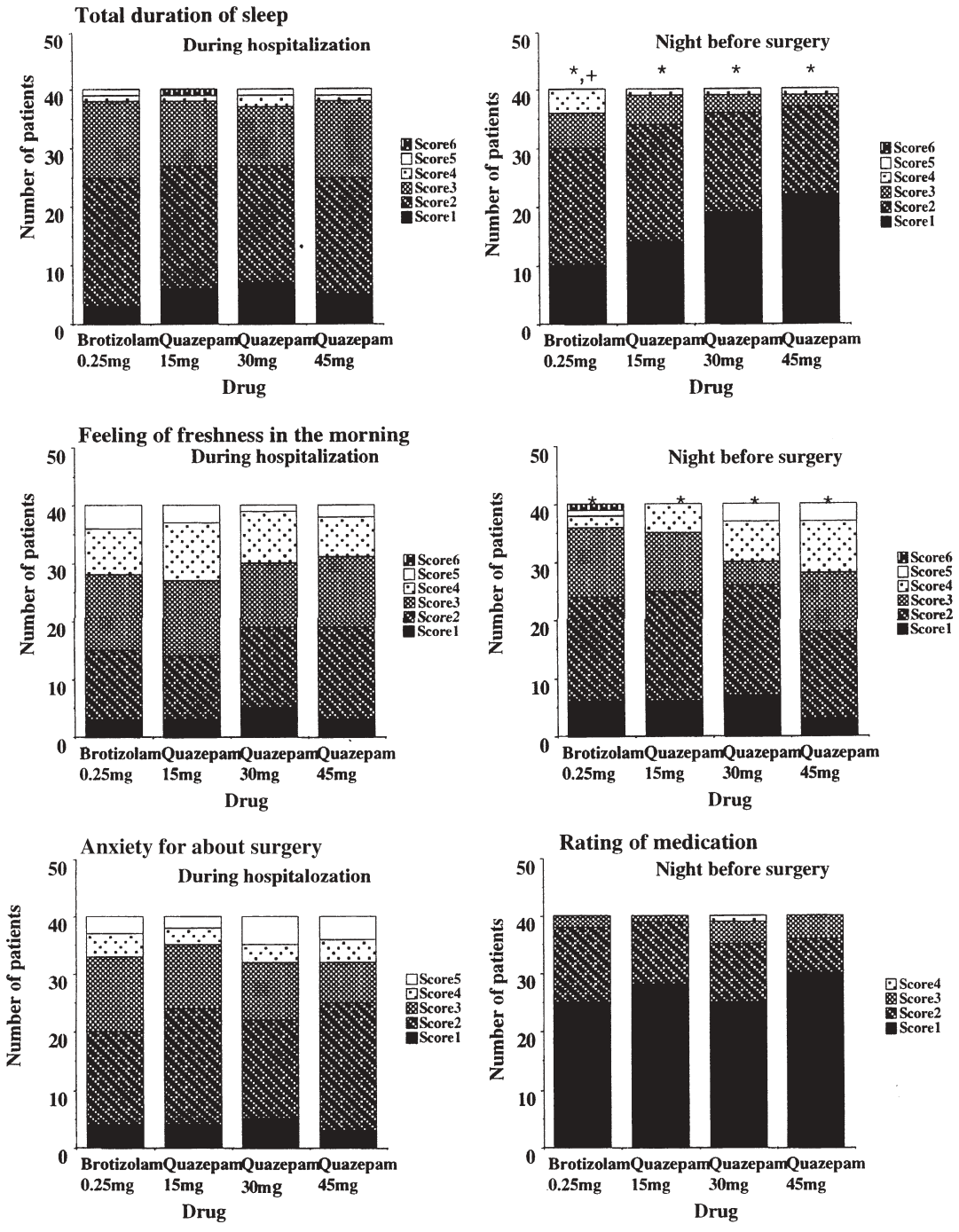


Fig. 1. Questionnaire ratings. $^{*}P < 0.05$ vs the control group; $^{+}P < 0.05$ vs during hospitalization; $^{\$}P < 0.05$ vs quazepam 30 mg and 45 mg

was given at the pre-anesthesia visit on the day before surgery and another questionnaire, for the pre-operative night, was given in the morning on the day of surgery.

In the first 8 patients who received quazepam 15 mg, 30 mg, and 45 mg, plasma concentrations of quazepam and its metabolites were measured 12 h after quazepam administration (at the time the patients entered the operating room). Venous blood (5 ml) was drawn and the plasma concentration was measured by high-performance liquid chromatography (LC-10A, SPD-10A; Shimazu, Kyoto, Japan).

Statistical analysis was performed with the χ^2 test and Student's *t*-test for patient backgrounds, and the

Kruskal—Wallis test and Mann Whitney test were used to compare the groups. The ratings on the questionnaire for the periods during hospitalization and the night before surgery were compared with the Wilcoxon signed rank test. Plasma concentrations were analyzed by analysis of variance, followed by the Student-Newman-Keuls post-hoc test. A P value of less than 0.05 was considered to be statistically significant.

Results

The demographic data of the patients were not different among the five groups (Table 1).

The sleep quality during hospitalization was comparable in the five groups (Fig. 1). The speed of falling asleep, sleeping state, and feeling of freshness in the morning on the night before surgery were improved in all the drug-administered groups compared to the control group, and compared to these characteristics during hospitalization (Fig. 1). The frequency of nocturnal awakening and dreaming decreased, and the total duration of sleep were increased on the night before surgery in all the drug-administered groups compared to the control group and compared to these characteristics during hospitalization (Fig. 1). The total duration of sleep was significantly longer in the quazepam 30 mg and 45 mg groups than in the control and brotizolam 0.25 mg groups (Fig. 1).

The plasma concentrations of quazepam and N-desalkyl-2-oxoquazepam (M6) 12 h after quazepam administration increased dose-dependently (Fig. 2).

Discussion

Quazepam 15 mg, 30 mg, or 45 mg, or brotizolam 0.25 mg administered at night before surgery improved night sleep compared to no medication. Quazepam 30 mg and 45 mg increased the total duration of sleep compared to brotizolam 0.25 mg.

Quazepam 30 mg improved the total duration of sleep, the quality of sleep, and patients' evaluations of sleep parameters [5]. Quazepam 15 mg had greater hypnotic activity and produced better sleep quality than placebo [6]. Similarly, brotizolam increased total sleep time and reduced the number of nocturnal awakenings [7]. There has been, however, no study comparing the effects of quazepam and brotizolam. Scharf [8] reported that clinicians' global evaluations of the effects of quazepam 15 mg and triazolam 0.5 mg (a short-acting drug like brotizolam), on insomnia were similar. Therefore, quazepam was expected to be effective for good sleep as a short-acting hypnotic. This was confirmed from the present results.

Quazepam has no rebound effects [9], and has less potential for ataxia, paradoxical excitation, and tolerance than flurazepam [10]. While we did not study side-effects precisely, we could not see any observable side-effects in the present study. Quazepam induced a

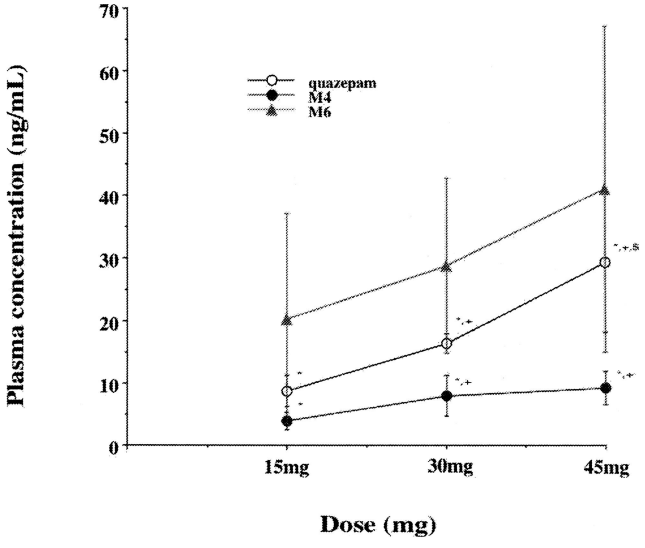


Fig. 2. Plasma concentrations of quazepam and its metabolites. *M4*, 2-oxoquazepam; *M6*, N-desalkyl-2-oxoquazepam; means ± SD. $^{*}P < 0.05$ vs M6; $^{+}P < 0.05$ vs 15 mg; $^{\$}P < 0.05$ vs 30 mg

Table 1. Backgrounds of the patients

	Control	Brotizolam 0.25 mg	Quazepam 15 mg	Quazepam 30 mg	Quazepam 45 mg
Age (years)	53 ± 10	52 ± 13	56 ± 12	49 ± 14	54 ± 15
Male/Female	16/24	14/26	17/23	15/25	18/22
Body weight (kg)	61.2 ± 12.5	56.9 ± 18.9	60.3 ± 16.2	58.5 ± 14.2	59.4 ± 12.7
Duration of surgery (min)	264 ± 85	272 ± 105	308 ± 97	249 ± 111	285 ± 132
Surgery					
Upper abdomen	14	9	12	9	13
Lower abdomen	10	10	11	12	10
Chest	9	9	10	11	8
Craniofacial	7	12	7	8	9

Mean ± SD values or numbers of patients are shown

sleep pattern on electroencephalograms and reduced the induction time to sleeping, without causing muscle relaxation, in contrast to diazepam [11]. Quazepam 50 mg inhibited rapid eye movement (REM) sleep, but REM sleep was not inhibited with 10 mg and 25 mg quazepam [12]. In addition, both stage 1 and slow-wave sleep (stages 3 and 4) were decreased by quazepam [13]. Brotizolam 0.25 to 0.5 mg did not change REM sleep [14]. The mechanisms of these differences between quazepam and other benzodiazepines are not known. Quazepam and one of its major metabolites, 2-oxoqnazepam (M4), have been demonstrated to be selective for the benzodiazepine 1 receptor, whereas other benzodiazepines show a similar affinity for benzodiazepine 1 and 2 receptors [15]. Therefore, side effects such as rebound effects, ataxia, paradoxical excitation, and tolerance might be related to the benzodiazepine 2 receptor, while the benzodiazepine 1 receptor is responsible for sleep, especially REM sleep.

M4 and M6 are active metabolites of quazepam. The elimination half-life of quazepam was shown to be 27 to 41 h, that of M4 was 40 h, and that of M6 was 70 to 75 h [16]. There has been no study showing the relation of plasma quazepam concentrations to its hypnotic effects. However, the brain level of quazepam was reported to parallel the plasma level [17]. We can say that no sedation occurred on the next morning with quazepam 45 mg when the plasma quazepam concentration was 30 to 65 $ng \cdot ml^{-1}$.

In the treatment of insomnia, daytime sedation increased with quazepam 30 mg compared to 15 mg [18]. Brotizolam at doses below 0.5 mg at night usually produced minimal morning drowsiness; no residual impairment of psychomotor performance occurred following doses within the recommended range of 0.125 to 0.25 mg [19], because of its short half-life (3.6 to 7.9 h) [20]. In the present study, no patients were drowsy with an M6 concentration higher than 40 $ng \cdot ml^{-1}$. In the presence of quazepam and M4, M6 is reported not to contribute extensively to the observed pharmacological activity [17].

If quazepam has some daytime sedative effects, the dose of sedatives during anesthesia may be decreased and the sedative effects of quazepam may delay emergence from anesthesia. However, we did not study the doses of anesthetics or the emergence time in the present study because we enrolled many patients in a short period during the same season, and anesthetics and anesthesia methods were not regulated. Therefore, the effects of a preoperative night hypnotic drug on anesthesia and postoperative management should be further studied to confirm the usefulness of such drugs.

In conclusion, as preoperative night hypnotic drugs, quazepam 15 to 45 mg improved night sleep, as did brotizolam 0.25 mg, while quazepam 30 mg and 45 mg increased the total duration of sleep more than brotizolam 0.25 mg. No sedation occurred with quazepam plasma concentrations of 30 to 65 $ng \cdot ml^{-1}$.

Appendix

Questionnaire concerning sleep

A. Speed of falling asleep
   1. Very well 2. Fairly well
   3. Somewhat good 4. Somewhat bad
   5. Fairly bad 6. Very bad

B. Sleeping state
   1. Very deep 2. Fairly deep
   3. Light sleep 4. Almost no sleep

C. Frequency of nocturnal awakening
   1. None 2. Once
   3. Twice 4. Three times or more

D. Frequency of dreaming
   1. No dreams 2. May have dreamed
   3. Dreamed some
   4. Had many dreams

E. Total duration of sleep
   1. More than 8 hours 2. Between 6 and 8 hours
   3. Between 4 and 6 hours
   4. Between 2 and 4 hours
   5. Less than 2 hours 6. None

F. Feeling of freshness in the morning
   1. Got up feeling entirely refreshed
   2. Pretty refreshed
   3. Somewhat refreshed 4. Somewhat dull
   5. Pretty dull
   6. Feeling entirely dull

G. Anxiety about surgery (During hospitalization)
   1. No anxiety 2. Slightly anxious
   3. Somewhat anxious 4. Fairly anxious
   5. Considerably anxious

G. Rating of medication (No medication for the control group)
   1. Glad to haven taken (not taken)
   2. Fairly glad to have taken (not taken)
   3. Some regret for having taken (not taken)
   4. Regret having taken (not taken)

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