Effects of Eszopiclone and Zolpidem on Sleep and Waking States in the Adult Guinea Pig

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Study Objective: The present study was designed to compare and contrast the effects of eszopiclone and zolpidem on the states of sleep and wakefulness in chronically instrumented, unanesthetized adult guinea pigs.

Design: Adult guinea pigs were implanted with electrodes to record sleep and waking states and to perform a frequency analysis of the EEG. Eszopiclone (1 and 3 mg/kg) and zolpidem (1 and 3 mg/kg) were administered intraperitoneally.

Measurements and Results: The administration of eszopiclone (1 and 3 mg/kg) resulted in a significant dose-dependent increase in NREM sleep. Zolpidem produced a significant increase in NREM sleep, but only at a dose of 3 mg/kg. The following changes in NREM and REM sleep, as well as in the power spectra, were all significant when the effects of 1 and 3 mg/kg of eszopiclone were compared with responses induced with 1 and 3 mg/kg of zolpidem, respectively: The increase in NREM sleep produced by eszopiclone was greater than that following the administration of zolpidem. The mean latency to NREM sleep following the administration of eszopiclone was significantly shorter than zolpidem. Eszopiclone significantly increased the latency to REM sleep. The mean duration of episodes of NREM sleep was increased by eszopiclone, but not by zolpidem. The EEG power increased in the delta band and decreased in the theta band during NREM sleep following the administration of eszopiclone. No significant changes occurred in any of the frequency bands analyzed following zolpidem administration.

Conclusions: The differences in the effects of eszopiclone and zolpidem on sleep and waking states and the power spectra of the EEG likely reflect the fact that eszopiclone and zolpidem bind to different subunits of the GABA subunit receptor complex.

Keywords: Hypnotics; NREM sleep; Wakefulness; EEG power; GABA subunit receptor

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CLASSIC HYPNOTICS, SUCH AS THE BENZODIAZEPINES, WHICH ARE AGONIST MODULATORS OF GABA RECEPTORS, HAVE BEEN WIDELY USED AS A TREATMENT FOR INSOMNIA. However, these drugs have deleterious side effects, such as anterograde amnesia; when used chronically they have the potential to produce tolerance, dependence, and withdrawal pathologies such as rebound insomnia. Behavioral studies in animals have shown that these drugs also disrupt sleep architecture and suppress REM sleep.

In an attempt to minimize the adverse effects of benzodiazepines, new-generation nonbenzodiazepine hypnotics have been developed, such as zopiclone, a cyclopyrrolone derivative, and zolpidem, an imidazopyridine derivative, which are short-acting and are structurally different from the benzodiazepines. These nonbenzodiazepine hypnotics act by potentiating the benzodiazepine-GABA receptor complex in the same manner as the benzodiazepines. However, zopiclone binds to the benzodiazepine-GABA receptor complex on a site that is near to, but distinct from, the benzodiazepine site, i.e., it exhibits a similar affinity for the GABA subunit and zolpidem receptors. alpha1 subunits as the benzodiazepines, but it also activates alpha3 and alpha5 subunits. Recent receptor binding studies have shown that zolpidem displays a significantly low affinity for the alpha2 and alpha3 subunits and almost no activity at the alpha5 subunits, which is different from the binding properties of zopiclone and the benzodiazepines.

Although a number of studies have described the hypnotic effects of zopiclone and zolpidem in experiment animals, there are no reports that have provided quantitative data that compare and contrast the effects of eszopiclone (s-isomer of zopiclone, a racemic mixture) and zolpidem on the states of sleep and wakefulness in a single species under identical experimental conditions. The only study that examined both compounds used extremely high doses of zopiclone and zolpidem (20 and 100 mg/kg), respectively. In our study, doses of eszopiclone and zolpidem were used that are within the range of those typically employed when these substances are administered as hypnotics. In addition, the effects of zopiclone and zolpidem on sleep and wakefulness were examined in the guinea pig because there are no studies reporting the effects of these hypnotics in this species (which is unique because guinea pigs can be employed to carry out research involving chronic and acute in vivo experiments as well as in vitro slice studies—see Discussion). Therefore, the objectives of the present report were to characterize and compare the hypnotic actions of eszopiclone and zolpidem in the adult guinea pig. To achieve these objectives, we examined the effects of the intraperitoneal injection of eszopiclone and zolpidem (at 1 and 3 mg/kg) on sleep and waking states as well as on EEG power in chronically instrumented, unanesthetized guinea pigs.
METHODS

Animals and Surgical Procedures

Adult guinea pigs (500-870 g; n = 5), obtained from and determined to be in good health by the VA Greater Los Angeles Healthcare System (VAGLAHS), were used in the present study. All procedures were conducted in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals and approved by the Animal Research Committee of the VAGLAHS. All efforts were made to minimize the number of animals used in this study. Animals were housed in a temperature (22 ± 1 °C) and humidity (50%-70%) controlled environment with a 12:12-h light/dark cycle (lights on from 6:00-18:00); the animals had ad libitum access to food and water.

The animals were prepared for monitoring the behavioral states of sleep and wakefulness and for determining the effects of intraperitoneally administered eszopiclone and zolpidem. Briefly, under ketamine/xylazine (45/5 mg/kg, im) anesthesia, using sterile surgical procedures, guinea pigs were implanted with electrodes for recording the cortical electroencephalogram (EEG), the electrooculogram (EOG), and the electromyogram (EMG). A Winchester plug, connected to these electrodes, and a chronic head-restraining device were bonded to the calvarium with acrylic cement. Following surgery, antibiotics were administered both systemically and topically.

After recovery from surgery, all guinea pigs were placed in a head-restraining apparatus and adapted to the recording environment each day for at least 2 weeks; thereafter, the animals exhibited spontaneous periods of wakefulness, NREM sleep, and REM sleep.

Drug Administration

In experimental sessions, all of which were conducted between 11:00 and 16:00, eszopiclone (Sepracor Canada Ltd; Windsor, Canada) or zolpidem (Sanofi-Aventis USA, Bridgewater, NJ) was administered intraperitoneally at doses of 1 and 3 mg/kg (0.5 mL); vehicle (50 mM acetate buffer solution, pH 4.5, 0.5 mL) was injected as a control. Injections were made during the first 10 min of each experimental session. Each animal received injections of all doses of both drugs and vehicle in a randomized protocol. A maximum of 2 injections of each dose of eszopiclone, zolpidem, or vehicle was made in each animal, and each injection was separated by at least 2 days.

Recording and Data Analysis

Polygraphic records were digitized and recorded using a Macintosh computer running AxoGraph X software (AxoGraph Scientific, Sydney, Australia). The behavioral states of wakefulness, NREM sleep and REM sleep were scored according to standard polygraphic criteria. Polygraphic recordings, which were divided into 30-s epochs, were used to construct hypnograms of waking and sleep states. The following dependent variables were determined based upon polygraphic data and behavioral observations during each recording session: (1) percentage of time spent in wakefulness, NREM sleep, and REM sleep following the injection; (2) latency to the onset of the first episode of each behavioral state, measured from the beginning of the injection; (3) number of episodes of each behavioral state per h (frequency); and (4) duration of episodes of each behavioral state. A frequency analysis (fast Fourier Transform) of the EEG power was performed using AxoGraph X software for each state in 1 Hz bins from 0.5-30 Hz over a period of 2 h following the administration of drugs or vehicle. The EEG signals to be analyzed were truncated into successive 15-s time segments (epochs). The relative power (percent of total) was calculated in each of the following frequency bands: delta (0.5-4 Hz); theta (4-9 Hz); sigma (9-14 Hz); and beta (14-30 Hz). Experimental data are expressed as means ± SEM. The statistical significance of the difference between sample means was evaluated using completely randomized one-way analysis of variance (ANOVA). When indicated by a significant F statistic after a one-way ANOVA, post hoc comparisons with Scheffe method were used to determine the individual levels of significant differences between control (vehicle) and eszopiclone, between control and zolpidem, or between eszopiclone and zolpidem. The criterion chosen to discard the null hypothesis was P < 0.05.

RESULTS

Data from 33 days of recordings were analyzed in conjunction with the intraperitoneal injections of drugs in guinea pigs in order to examine the effects of eszopiclone and zolpidem on sleep and waking states. In addition, 10 days of recordings with control injections of vehicle were conducted in the same animals that received injections of the preceding drugs. In contrast to vehicle, injections of eszopiclone (1 and 3 mg/kg) or zolpidem (3 mg/kg) increased the time spent in NREM sleep during the first 2-h recording period following the administration of the drug. No statistically significant changes in the time spent in sleep or wakefulness during the 3rd and 4th hour compared with those after vehicle administration were observed in conjunction with either eszopiclone or zolpidem. These data indicate that the effects of eszopiclone and zolpidem were limited to changes that occurred during the first 2 h following their administration. Therefore, the following sections describe and compare quantitatively the effects of these 2 drugs on the states of wakefulness, NREM and REM sleep, as well as EEG power, during the first 2 h following the injection of these drugs.

Effects of Eszopiclone and Zolpidem on the Percentage of Time Spent in Sleep and Waking States

The effects of the administration of eszopiclone and zolpidem on the percentage of time spent in sleep and waking states during the first 2 h following their injection are presented in Figure 1. ANOVA revealed a significant drug effect on the percentage of time spent in NREM sleep and waking states following the administration of eszopiclone or zolpidem (NREM sleep: df = 4,38, F = 21.31, P < 0.0001; wakefulness: df = 4,38, F = 20.61, P < 0.0001). Compared to the percentage observed following the injection of vehicle (n = 10), the administration of eszopiclone at 1 mg/kg and 3 mg/kg significantly increased the time spent in NREM sleep by 59.9% and 81.1% (vehicle: 29.7% ± 1.7%, n = 10; 1 mg/kg eszopiclone: 47.5% ± 1.3%,
Effects of Eszopiclone and Zolpidem on the Latency to Sleep

The effects of eszopiclone and zolpidem were also assessed by measuring the latency to the onset of the first episode of NREM sleep and REM sleep (Figure 2). Because injections of both drugs were made during wakefulness, there was no measure of the latency of wakefulness. ANOVA revealed significant drug effects on the latency of both NREM sleep and REM sleep (NREM sleep: df = 3.38, F = 15.72, P < 0.0001; REM sleep: df = 4.38, F = 6.10, P = 0.0007).

The mean latency of NREM sleep following the injection of eszopiclone at 1 mg/kg and 3 mg/kg was significantly shorter than vehicle-injected controls (1 mg/kg eszopiclone vs vehicle, P = 0.0007; 3 mg/kg eszopiclone vs vehicle, P = 0.0001; post hoc Scheffe method). Both doses of eszopiclone also significantly increased the mean latency to REM sleep (1 mg/kg eszopiclone vs vehicle, P = 0.0402; 3 mg/kg eszopiclone vs vehicle, P = 0.0015, post hoc Scheffe method).

Although there was a tendency for a decrease in the latency to NREM sleep and an increase in the latency to REM sleep following the injection of zolpidem at 3 mg/kg, neither dose of zolpidem significantly reduced the mean latency to NREM sleep or increased the latency to REM sleep. Moreover, the mean latency to NREM sleep following the injection of eszopiclone at 1 and 3 mg/kg was significantly shorter than that after

n = 10, P < 0.0001; 3 mg/kg eszopiclone: 53.8% ± 3.4%, n = 9, P < 0.0001; post hoc Scheffe method), and reduced the time spent in wakefulness by 24.8% and 34.1% (vehicle: 69.0% ± 1.8%, n = 10; 1 mg/kg eszopiclone: 52.0% ± 1.4%, n = 10, P < 0.0001; 3 mg/kg eszopiclone: 45.5% ± 3.5%, n = 9, P < 0.0001; post hoc Scheffe method), respectively.

No significant effects on the percentage of time spent in sleep and wakefulness were observed following the administration of zolpidem at 1 mg/kg. However, at doses of 3 mg/kg, zolpidem significantly increased the percentage of time spent in NREM sleep by 32.0% (39.2% ± 2.8%, n = 9, P = 0.0431, post hoc Scheffe method) and decreased the time spent in wakefulness by 13.0% (60.0% ± 1.9%, n = 9, P = 0.0423, post hoc Scheffe method).

Post hoc analyses also showed a significant difference in the percentage of time spent in NREM sleep and wakefulness following the administration of eszopiclone compared to NREM sleep and wakefulness following zolpidem administration. The increase in the percentage of time spent in NREM sleep and the decrease in the time spent in wakefulness following the administration of eszopiclone at 1 mg/kg were significantly greater than the time spent in NREM sleep and wakefulness after zolpidem administration at 1 mg/kg (NREM sleep: P = 0.0007; wakefulness: P = 0.0009; post hoc Scheffe method). The increase in the percentage of time spent in NREM sleep and the decrease in the time spent in wakefulness following the administration of eszopiclone at 3 mg/kg were significantly greater than the time spent in NREM sleep and wakefulness after zolpidem administration at 1 and 3 mg/kg, respectively (NREM sleep: 3 mg/kg eszopiclone vs 1 mg/kg zolpidem, P < 0.0001, 3 mg/kg eszopiclone vs 3 mg/kg zolpidem, P = 0.0032; wakefulness: 3 mg/kg eszopiclone vs 1 mg/kg zolpidem, P < 0.0001, 3 mg/kg eszopiclone vs 3 mg/kg zolpidem, P = 0.0036; post hoc Scheffe method).

There was no significant reduction in the time spent in REM sleep following the injection of eszopiclone or zolpidem at any doses (df = 4.38, F = 0.86, P = 0.4948, ANOVA).

Figure 1—The mean percentage of time spent in wakefulness, NREM sleep and REM sleep during the first 2-h period following the administration of eszopiclone, zolpidem, and control vehicle. Compared to the percentages observed following the injection of vehicle (n = 10), the administration of eszopiclone (1 mg/kg [n = 10] and 3 mg/kg [n = 9]) resulted in a significant increase in NREM sleep and a decrease in wakefulness. However, no significant effects were observed following the administration of zolpidem at 1 mg/kg (n = 5). Zolpidem significantly increased NREM sleep and decreased wakefulness at doses of 3 mg/kg (n = 9). Note that the increase in the percentage of time spent in NREM sleep following the administration of eszopiclone at 1 or 3 mg/kg was significantly greater than the time spent in NREM sleep after zolpidem administered at either 1 mg/kg or 3 mg/kg. The decrease in the time spent in wakefulness following the administration of eszopiclone at 1 or 3 mg/kg was also significant greater than the time spent in wakefulness after zolpidem administration at 1 or 3 mg/kg. Each bar represents the mean value; error bars indicate the SEM of each population. *P < 0.05, **P < 0.01, ***P < 0.001 vs vehicle control group. +++P < 0.001 vs 1 mg/kg zolpidem group. ##P < 0.01 vs 3 mg/kg zolpidem group by post hoc Scheffe method.
Effects of Eszopiclone and Zolpidem on the Duration of Episodes of Sleep and Waking States

Figure 2—Effects of the administration of eszopiclone and zolpidem on the latency to NREM sleep and REM sleep. Both doses of eszopiclone (1 and 3 mg/kg) significantly reduced the latency to NREM sleep and increased the latency to REM sleep. However, zolpidem at 1 and 3 did not significantly reduce the latency to NREM sleep, and did not increase the latency to REM sleep. Note that eszopiclone (1 and 3 mg/kg) resulted in a decrease in the mean latency to NREM sleep, which was significantly shorter than the latency after zolpidem administration (1 and 3 mg/kg). Each bar represents the mean value; error bars indicate the SEM of each population. *P < 0.05, **P < 0.01, ***P < 0.001 vs vehicle control group. +++ P < 0.001 vs 1 mg/kg zolpidem group. # P < 0.05, ## P < 0.01 vs 3 mg/kg zolpidem group by post hoc Scheffe method.

Effects of Eszopiclone and Zolpidem on Spectral EEG Power

The effects of eszopiclone and zolpidem on the relative EEG power during NREM sleep were examined in the 2-h period after the administration of these drugs. Figure 4 presents plots of relative EEG power density during NREM sleep following the injection of eszopiclone, zolpidem, and vehicle. ANOVA revealed significant drug effects on the relative EEG power in the delta and theta bands during NREM sleep following the injection of eszopiclone and zolpidem (the delta band: \( df = 4,38; F = 4.38; P = 0.0006 \); the theta band: \( df = 4,38; F = 12.13; P < 0.0001 \)).

Compared to control injections, both doses of eszopiclone at 1 mg/kg and 3 mg/kg significantly increased the relative power of the EEG in the delta band (vehicle: 36.0% ± 0.7%, n = 10; 1 mg/kg eszopiclone: 39.8% ± 1.1%, n = 10, P = 0.0251; 3 mg/kg eszopiclone: 40.6% ± 0.6%, n = 9, P = 0.0056; post hoc Scheffe method), and reduced the relative EEG power in the theta band (vehicle: 24.0% ± 0.4%, n = 10; 1 mg/kg eszopiclone: 22.3% ± 0.2%, n = 10, P = 0.0035; 3 mg/kg eszopiclone: 22.1% ± 0.3%, n = 9, P = 0.0011; post hoc Scheffe method), respectively. The EEG power in the sigma and beta bands were not significantly affected following the administration of eszopiclone at 1 mg/kg and 3 mg/kg.

In contrast, there were no significant changes in EEG power in any of the frequency bands analyzed during NREM sleep following zolpidem administration at doses of 1 or 3 mg/kg.
Post hoc analyses revealed that eszopiclone administration at 3 mg/kg significantly increased the relative power of the EEG in the delta band compared to that after zolpidem administration at 1 and 3 mg/kg (3 mg/kg eszopiclone vs 1 mg/kg zolpidem, P = 0.024; 3 mg/kg eszopiclone vs 3 mg/kg zolpidem, P = 0.013, post hoc Scheffe method). In addition, eszopiclone administration at 1 and 3 mg/kg significantly reduced the relative power of the EEG in the theta band compared to that after zolpidem administration at all doses (1 mg/kg eszopiclone vs 1 mg/kg zolpidem, P = 0.0001; 1 mg/kg eszopiclone vs 3 mg/kg zolpidem, P = 0.020; 3 mg/kg eszopiclone vs 1 mg/kg zolpidem, P < 0.0001; 3 mg/kg eszopiclone vs 3 mg/kg zolpidem, P = 0.021; post hoc Scheffe method).

DISCUSSION

The sleep cycle of guinea pigs is well known; in these animals, there is almost an equal distribution of sleep between day and night.24-26 The percentage of NREM sleep is approximately 30%. Of the total sleep time, 13% is occupied by REM sleep, a value similar to that which occurs in rats.27

The guinea pig is an especially useful species for research purposes because it can be utilized in numerous coordinated multidisciplinary sleep studies, ranging from those involving cellular mechanisms to others that are purely behavioral; such studies cannot be carried out in any other single species.28 For example, slice experiments are performed almost exclusively in neonatal rats, but not in adult rats or cats of any age. As a precocial species, guinea pigs display the same percentage of sleep from birth to death.24-29 This is important when performing in vitro experiments, because the mechanisms responsible for sleep and wakefulness are well developed in newborn guinea pigs. Chronic extracellular as well as intracellular recording studies during the states of sleep and wakefulness in the guinea pig can be correlated with the data obtained from the slice preparation; it is not possible to carry out such studies in rats, mice, or cats—in none of these species can one compare in vivo and in vitro studies of mature adult mechanisms controlling sleep and waking states. In addition, the discovery of similarities in sleep mechanisms in this species compared with others will reinforce the importance of the preservation of the processes in question; differences would provide new perspectives on how the nervous system controls sleep and wakefulness.

In the following sections, the effects of eszopiclone and zolpidem on the states of sleep and wakefulness are discussed and compared with data obtained from other species. The effects of eszopiclone and zolpidem are also discussed on the basis of their differential binding properties vis-à-vis subunits of the GABA\_A receptor complex.

Differential Binding Properties of Eszopiclone and Zolpidem

The differences observed between the effects of eszopiclone and zolpidem in guinea pigs likely reflect the fact that these 2 hypnotics bind to different subunits of the GABA\_A receptor complex. Eszopiclone is a cyclopyrrolone derivative and an enantiomer of zopiclone. Although not fully elucidated, in vitro studies with functional recombinant GABA\_A receptors demonstrate that zopiclone, and presumably eszopiclone, show similar binding profiles to the \(\alpha1\) subunit of the GABA\_A receptor as benzodiazepines, but also display considerable activity at GABA\_A receptors containing the \(\alpha3\) subtype as well as \(\alpha5\) subtype.13,14,30 Among the 6 known \(\alpha\)-subtypes, \(\alpha1\) and \(\alpha3\) have been associated with brain systems that control sleep.31

Zolpidem, an imidazopyridine derivative, appears to possess a very high affinity for the GABA\_A receptor \(\alpha1\) subunit, and more precisely binds the \(\alpha1\beta2\gamma2\) subunits with the highest affinity.12,33 It has significantly less affinity for the \(\alpha2\) and \(\alpha3\)
and increased the latency to REM sleep. Finally, there was a significant increase in duration of episodes of NREM sleep and a decrease in duration of episodes of wakefulness. These changes indicate that the increase in the percentage of time spent in NREM sleep and the decrease in wakefulness were due to the significant changes induced by eszopiclone in the duration of episodes of NREM sleep and wakefulness, respectively.

It is generally accepted that the consolidation of sleep, especially episodes of NREM sleep, are associated with a number of therapeutic benefits; conversely, there are negative consequences when sleep is fragmented. Therefore, the consolidation of sleep, which is reflected by the presence of long duration episodes of NREM sleep, is a possible beneficial attribute of eszopiclone.

Figure 4—Effects of eszopiclone and zolpidem on the power spectra of the EEG of the frontal cortex during NREM sleep in the 2-h period after the administration of these drugs. Representative spectral analyses of the EEG are shown following the injection of eszopiclone (A) and zolpidem (B). The mean values of the relative power of delta, theta, sigma, and beta frequency bands from the frontal cortex following the injection of eszopiclone and zolpidem are presented in C to F. Both doses of eszopiclone (1 and 3 mg/kg) significantly increased the relative power of the EEG in the delta band and reduced EEG power in the theta band. There were no significant changes in EEG power during NREM sleep following zolpidem administration at 1 or 3 mg/kg. *P < 0.05, **P < 0.01 vs the vehicle control group. + P < 0.05, +++ P < 0.001 vs 1 mg/kg zolpidem group. # P < 0.05 vs 3 mg/kg zolpidem group by post hoc Scheffe method.

The Effects of Eszopiclone on Sleep and Waking States

The administration of eszopiclone resulted in significant changes in NREM sleep at doses of 1 and 3 mg/kg consisting of an increase in the amount of time spent in NREM sleep. This increase was accompanied by a significant decrease in wakefulness and in the duration of episodes of this state. No significant effects on the time spent in REM sleep were observed, although eszopiclone tended to reduce the amount of REM sleep. Eszopiclone significantly reduced the latency to NREM sleep and increased the latency to REM sleep. Finally, there was a significant increase in duration of episodes of NREM sleep and a decrease in duration of episodes of wakefulness. These changes indicate that the increase in the percentage of time spent in NREM sleep and the decrease in wakefulness were due to the significant changes induced by eszopiclone in the duration of episodes of NREM sleep and wakefulness, respectively.

It is generally accepted that the consolidation of sleep, especially episodes of NREM sleep, are associated with a number of therapeutic benefits; conversely, there are negative consequences when sleep is fragmented. Therefore, the consolidation of sleep, which is reflected by the presence of long duration episodes of NREM sleep, is a possible beneficial attribute of eszopiclone.
These preceding data are generally consistent with findings in other experimental animals and in humans. In rats, zopiclone, administered intraperitoneally in doses from 2.5 to 10 mg/kg, was found to increase NREM sleep, decrease wakefulness, decrease the latency to NREM sleep, and increase the latency to REM sleep; a decrease of the total time spent in REM sleep was similarly reported. A recent study in the rat showed that zopiclone also significantly increased NREM sleep in a dose-dependent manner but had no effects on REM sleep. At higher doses (20 and 100 mg/kg), zopiclone has a significant suppressing effect on REM sleep in addition to increasing the time spent in NREM sleep. In humans, zopiclone has been shown to have a positive effect on sleep with few adverse effects in a large number of studies in healthy subjects as well as in different groups of patients. The majority of these studies reported that zopiclone has mild hypnotic actions (consistent of an increase of NREM sleep, an increase in sleep consolidation, a decrease of NREM sleep onset latency, and a decrease or no change in REM sleep in normal subjects). However, some studies reported that zopiclone has little effect on NREM sleep in young healthy subjects, which probably reflects the large amount of NREM sleep present in these individuals. In subjects with insomnia, zopiclone increased NREM sleep with a decrease or no change in REM sleep.

There was a positive relationship between an increase in duration of NREM episodes and increase in EEG power of the delta frequency band, as well as a decrease in the theta band, during NREM sleep following the administration of eszopiclone at doses of 1 and 3 mg/kg. The magnitude of EEG slow wave activity in the delta band is considered to be an index of sleep intensity. Therefore, the increase in EEG delta power and in duration of episodes of NREM sleep following the administration of eszopiclone suggest that eszopiclone-induced sleep may be more “profound” than normal sleep. The enhancement of EEG power in the delta band by eszopiclone during NREM sleep is also supported by data from previous animal studies. Spectral analysis of the EEG in rabbits showed that zopiclone, at a dose of 2 mg/kg, significantly increased power in the delta frequency band and decreased power in the theta frequency band. In humans, zopiclone has been found to induce a minor increase in delta EEG power, a significant decrease in theta EEG power, and an increase in sigma EEG power. Other studies, however, reported that zopiclone decreases the power density in other ranges of frequencies (such as <10 Hz) and enhances the power density in the frequency range of 12-15 Hz.

**The Effects of Zolpidem on Sleep and Waking States**

Zolpidem produced significant changes in sleep and waking states, but only at a dose of 3 mg/kg. It increased the percentage of time spent in NREM sleep, which was accompanied by a significant decrease in wakefulness. No significant effects of zolpidem on the time spent in REM sleep were observed. In addition, there were no significant changes in EEG power in any of the frequency bands analyzed during NREM sleep following zolpidem administration.

Our results are generally in accordance with data from previous animal studies. Experiments in rats showed that zolpidem, administered intraperitoneally at a high dose of 10 mg/kg during the dark period, increased NREM sleep and the mean duration of episodes of NREM sleep, but did not affect REM sleep. Other studies in the rat reported that zolpidem administered orally, at doses of 3 mg/kg or higher, increased NREM sleep during the light period. Another study in the rat showed that the latency to NREM is reduced following the administration of zolpidem at 2.5, 5, and 7.5 mg/kg; while the latency to REM sleep was only increased at the 2 higher doses, the amount of REM sleep decreased only at the highest dose. Previous data regarding the effects of zolpidem on EEG power during NREM sleep are discordant, showing either an increase in EEG power in the delta frequency band during NREM sleep or a reduction in EEG power in this band.

In normal human subjects, zolpidem exerts moderate effects on sleep. Studies in young healthy subjects found that zolpidem, given in dosages between 2.5 and 30 mg, shortens the latency to NREM sleep and has no consistent effect on the total sleep time or the number of episodes of wakefulness. However, the total time spent in NREM sleep was found to increase following the administration of zolpidem in chronic insomnia patients. A decrease in REM sleep and a prolonged latency to REM sleep following the administration of zolpidem was observed by Brunner et al., but not by Blois and Gaillard in healthy subjects nor by Monti and Monti in chronic insomniacs. Spectral analyses showed that zolpidem markedly reduced the power density of slow wave activity (<10 Hz) and enhanced the power density in the range of spindle frequencies during NREM sleep in young healthy subjects.

**Differences between the Effects of Eszopiclone and Zolpidem**

While the administration of either eszopiclone at doses of 1 and 3 mg/kg or zolpidem at doses of 3 mg/kg resulted in a significant increase in NREM sleep, the present quantitative analyses reveal significant differences in the effects of eszopiclone and zolpidem on sleep and waking states. For example, the increase in the percentage of time spent in NREM sleep and the decrease in the time spent in wakefulness following the administration of eszopiclone at 1 mg/kg and 3 mg/kg were significantly greater than the time spent in NREM sleep and wakefulness after zolpidem administration (which was present only at a dose of 3 mg/kg). In addition, eszopiclone, at doses of 1 and 3 mg/kg, resulted in a decrease in the mean latency to NREM sleep that was significantly shorter than that following the administration of zolpidem at either 1 or 3 mg/kg. Furthermore, eszopiclone significantly increased the mean duration of episodes of NREM sleep, whereas zolpidem did not produce any significant change in the mean duration of episodes of NREM sleep. Finally, there was a significant increase in EEG power in the delta band and a decrease in EEG power in the theta band during NREM sleep following the administration of eszopiclone at both 1 and 3 mg/kg. In contrast, there were no significant changes in EEG power in any of the frequency bands analyzed during NREM sleep following zolpidem administration at 1 or 3 mg/kg. Therefore, the present data suggest that, in the guinea pig, eszopiclone has a greater effect on NREM sleep and the generation of NREM delta activity than zolpidem.

In summary, the present results demonstrate that eszopiclone, compared with zolpidem, has a pharmacological profile in the adult guinea pig that is principally characterized by a
more rapid onset of hypnotic action and an increased amount of time spent in NREM sleep; eszopiclone also produced an increase in EEG delta power, whereas zolpidem had no effect on delta activity. In addition to potential differences in uptake and distribution properties, we suggest that the relative binding properties of these 2 drugs may account for the differences in their effects on the states of sleep and wakefulness as well as the power spectra of the EEG.

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