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Sleep Promoting Substances

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SUMMARY

Adequate sleep is essential to the maintenance of alertness during continuous and sustained operations, and sleep promoting substances or hypnotics have been used successfully in support of demanding scenarios extending over many weeks. The rest periods during such operations are limited in duration and occur at intervals throughout the 24-hour cycle. There are many hypnotics now available, but the necessary profile is limited to a few drugs. These are temazepam (10-20mg), zolpidem (10mg) and brotizolam (0.125-0.25mg). With each drug there is evidence of efficacy and limited duration of actions with the dose range recommended. Melatonin (5mg) also possesses hypnotic activity, with efficacy during the day similar to 20mg temazepam. However, whereas the benzodiazepines and related drugs possess hypnotic activity throughout the 24 hour cycle, it would appear that melatonin is only effective when the endogenous plasma levels of naturally occurring melatonin are low, and that ingestion at certain times of day may lead to sleep disturbance. The need to be aware of the constraints on the use of melatonin mitigates against its effectiveness in operations when missions will be required at all times of the day and night with rest periods scattered throughout the 24 hour cycle. As far as military operations are concerned the United Kingdom used the hypnotic temazepam (10-20mg) in Royal Air Force personnel during the South Atlantic campaign and during the liberation of Kuwait. It still remains the drug of choice for the Royal Air Force. The recent availability of ultra short acting hypnotics such as zaleplon (10mg) has raised the possibility of using hypnotics for shorter sleep periods than 6 hours.

INTRODUCTION

In the management of intensive and sustained operations the careful timing of work and rest periods may go a long way to avoid the decrements in performance associated with working for long periods which include duty overnight. However, after a few days it may be impossible to sustain sleep at acceptable quality. This may be due to a variety of reasons or to combinations of disturbing factors. For example, the time available for sleep may coincide with times which are not conducive to sleep, the presence of poor sleeping conditions or environmental factors associated with the mission such as noise, heat, uncomfortable posture may cause awakenings, or the overall stress and anxiety associated with the mission may disturb sleep. The greatest need for sleep is experienced between 2400 and 0600 and environmental clues normally encourage this. The quantity and quality of sleep are strongly dependent on the circadian phase; sleep taken during the day will be shorter and less recuperative than sleep taken at night. Although environmental factors during the day serve to accentuate this difference, even in rooms isolated from environmental factors sleep is less efficient during the day. It has been estimated that by the end of a week of night duty, the equivalent of at least one night's sleep may have been lost. While the duration of slow wave sleep is unchanged following night work, due to the duration of prior

wakefulness, stage 2 and REM sleep are reduced. When personnel are required to work at night this is at the lowest point in their circadian performance rhythm, strategies that can curtail the amount of sleep deprivation would be very beneficial. Work periods beginning in the early morning also lead to reduced sleep times. Because of the circadian peak in alertness it is difficult to retire to sleep early before an early shift. Lavie (1986) has described this time as the forbidden zone for sleep. Therefore even if the time is available for sleep if it is at the 'wrong' point in the circadian cycle personnel will be unable to take full advantage of the sleep opportunity. Working at night also exacerbates the age-related decline in sleep quality and quantity. Older subjects find it easier to adapt to early morning work periods. Commanders need to take these factors into account when planning work/rest schedules in operational conditions.

Under such circumstances it may be necessary to consider the use of hypnotic drugs to aid sleep. Some individuals appear to be able to sleep anywhere, at any time but others may be unable to gain any benefit from the time available for sleep. Adequate sleep is essential to the maintenance of alertness during continuous and sustained operations, and sleep promoting substances or hypnotics have been used successfully in support of demanding scenarios extending over many weeks.

HYPNOTICS

The largest class of hypnotics, the benzodiazepines, is known to speed sleep onset, reduce awakenings, and increase total sleep time in normal sleepers and those suffering from transient and chronic insomnia. In addition they may alter sleep architecture by delaying the appearance of rapid eye movement (REM) sleep, and increasing sleep spindles. The imadazopyridine zolpidem and the cycloprrolone zopiclone have similar effects on the EEG as benzodiazepines [Nicholson and Stone, 1983]. Zolpidem, however, may increase slow wave sleep, at least in young individuals and there is at least one report of a moderate increase in slow wave sleep with zopiclone [Nicholson and Stone, 1983]. Some have suggested that there is a special benefit to these newer nonbenzodiazepines. However the impact of drug induced changes in slow wave sleep is unknown. Essentially, the problems sleeping associated with sustained operations are characteristic of transient insomnia.

The rest periods during such operations are limited in duration and occur at intervals throughout the 24-hour cycle. It is, therefore, evident that the onset and duration of action of any hypnotic used in such circumstances are critical. Essentially these requirements demand a pharmacokinetic profile of rapid absorption and distribution / elimination rates which ensure freedom from residual effects within 6 hours of ingestion. There are many hypnotics now available, but the necessary profile is limited to a few drugs. These are temazepam (10-20mg), zolpidem (10mg) and brotizolam (0.125-0.25mg). With each drug there is also evidence of efficacy and limited duration of actions with the dose range recommended.

The key pharmacokinetic parameters of a range of hypnotic drugs are given below:

Key Pharmacokinetic Parameters

Therapeutic Agent	t_{max} (h)	t_½ (h)
Flurazepam	0.5–6	47–100*
Diazepam	0.5–2	20–80*
Temazepam	1–3	10–20
Oxazepam	2–3	4–20
Brotizolam	0.8–1.2	3–8
Zopiclone	1.0	3.5–6.5
Zolpidem	1.5	1.1–3.3
Zaleplon	1.0	0.9–1.1

*active metabolite

The mean elimination half-lives of brotizolam and zolpidem are around 5 h or less. Temazepam is a suitable hypnotic, which, although it has a longer half life, it has a relatively short duration of action due to the decrease in plasma levels as the drug is distributed from the central to the peripheral compartment. Zopiclone (3.75 – 7.5 mg) is also rapidly absorbed, but the activity of the recommended dose range extends beyond 6 hours. The limited duration of action of Temazepam, Brotizolam and Zolpidem has been shown in laboratory studies where a lack of residual effects on performance 6 hours after ingestion has been established. (Figures 1 & 2).

Change in Performance in Tracking vs Placebo

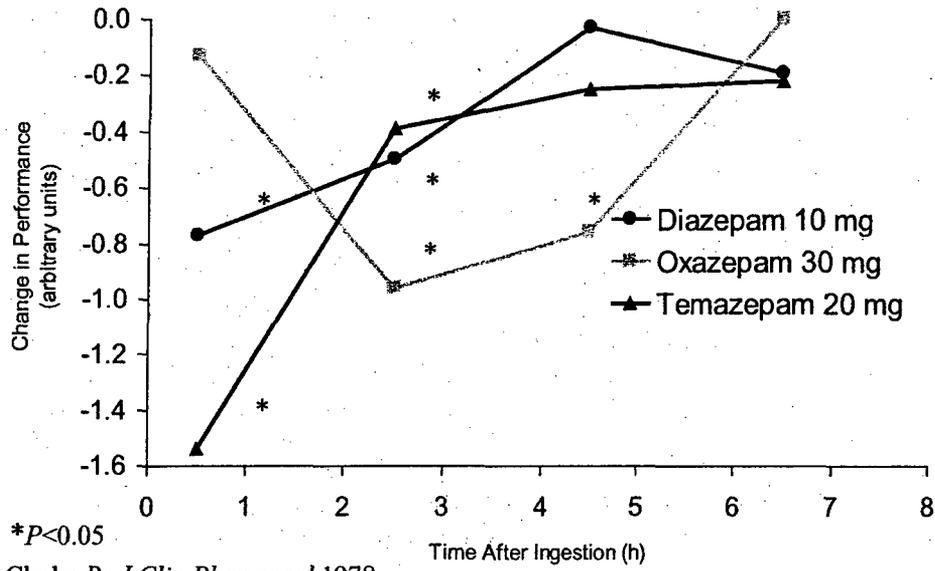


Figure 1

Residual Effects on Tracking vs Placebo

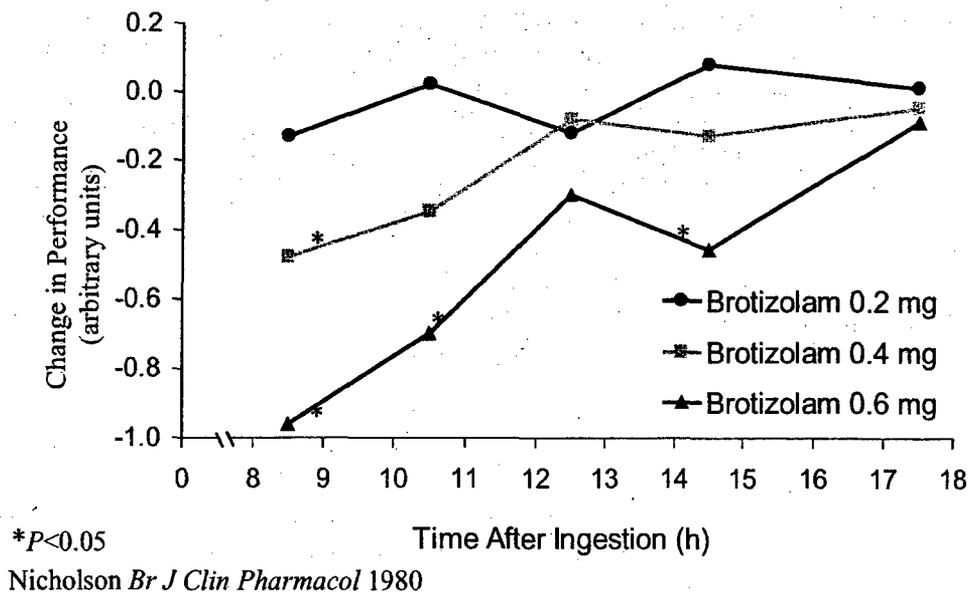


Figure 2

RESEARCH AT MILITARY ESTABLISHMENTS

The main centres for research into the potential use of hypnotics in sustained and continuous operations has been in research establishments or universities which have been supported by the military. These studies not only tell us about the drugs considered for use by the military, but also the circumstances and scenarios for their use. Hypnotics are used for critical sleep periods and some studies have combined the use of a stimulant with a hypnotic.

Studies on the efficacy and residual effects of hypnotics were carried out at one of the establishments, which was partially subsumed into QinetiQ, the RAF Institute of Aviation Medicine. This research during the 1970s and 1980s examined a number of hypnotic drugs and temazepam was selected as the drug of choice for aircrew. A rapidly absorbed formulation and a dose of 10 or 20 mg provided useful hypnotic activity without residual effects on performance or mood. It was also useful at inducing sleep during the day and for these reasons it has been used by both military and civil aircrew in the United Kingdom for the last 20 years. In particular it has been used in support of real intensive air operations [Baird et al, 1983, Nicholson et al 1985].

The Royal Australian Army Medical Corps have also carried out studies on the effects of temazepam (20mg) in relation to travel across time zones [Donaldson and Kennaway, 1991]. They reported a beneficial effect on sleep and alertness after transmeridian travel without adverse effects on performance. The rate of adjustment to the new time zone, however, was not increased. The Italian Air Force has also carried out studies on temazepam [Porcu et al., 1997]. Temazepam (20mg) was studied in individuals who were subjected to a rapid shift of their sleep / wake cycle. It was effective at inducing and maintaining sleep during the day and was not associated with any carry over effects.

Temazepam has therefore been proved to be a useful drug for those attempting to sleep at times in the circadian cycle when sleep is difficult and also under the difficult sleeping conditions (heat, flies, noise etc.) encountered under operational conditions on Ascension Island. Unfortunately, in the United Kingdom at least, temazepam has become a drug of abuse, and for this reason its use is controlled. In spite of changes in formulation some abusers still use temazepam, and an alternative drug free of medico-legal constraints is desirable. In this context zolpidem would appear to be a useful drug. Studies in the United Kingdom have shown that in male subjects it is free of residual effects on performance and is also an effective sleep inducer during the day [Nicholson and Pascoe, 1986]. Studies in France have also evaluated zolpidem (10mg) for its residual effects on daytime wakefulness in navy fighter pilots [Sicard et al, 1993], and showed that in the absence of residual effects, zolpidem could be considered for operational use. The use of zolpidem (10mg) to aid napping has been studied by the US Army Aeromedical Research Laboratory, Fort Rucker [Caldwell and Caldwell, 1998]. The authors considered that post nap impairments could compromise performance under operational conditions. Other data which suggests that zolpidem may have residual effects on performance in some individuals will be discussed.

Zopiclone has been tested in the United Kingdom [Nicholson and Stone, 1983] and has been shown to have residual effects on performance 9h after ingestion at the 7.5 mg dose. This dose is therefore unsuitable for those who carry out skilled work.

OTHER DRUGS

Alcohol is often considered to be a sleep promoting substance, however, although it may initially promote sleep onset it also has detrimental effects on sleep [Stone, 1980]. The amino acid tryptophan has been reported to increase total sleep time on the first night after westward transmeridian travel [Spinweber, 1987] but its effects on sleep are generally considered to be unpredictable and limited [Nicholson et al., 1994].

A number of other drugs used to treat a range of medical conditions also possess sleep-inducing properties. The effects of H1 antihistamines on subjective and objective sleepiness and

performance have been widely studied. The first generation antihistamines are lipophilic, cross the blood-brain barrier with ease and have poor receptor selectivity, sedation is a major side effect of these drugs and their use in the treatment of allergy has been largely replaced by the second generation drugs which do not have these problems. In particular diphenhydramine is particularly sedating and for this reason is the main ingredient in many over-the counter sleeping aids. Promethazine is another sedating antihistamine, which is included in cold and influenza remedies, which are taken at night. Its sedating properties are also used when it is included as an active control in studies of the sedating and performance effects of a range of drugs. The use of these drugs in continuous and sustained operations has not been tested. However, it is possible that individuals who can buy them easily in their local pharmacist use them.

Many antidepressant drugs improve sleep. However, this sedation is accompanied by alteration of the sleep cycle such as suppression of REM sleep and performance deficits. Therefore, these drugs are considered unsuitable for use as a sleep inducer in those carrying out skilled work. Lithium improves nocturnal sleep but is also associated with cognitive deficits and is unsuitable for use in military personnel.

MELATONIN

Melatonin is a naturally occurring substance and for this reason has been considered to be a natural sleep inducing substance. There is therefore much interest concerning the activity of melatonin and how melatonin may be used to alleviate disturbances of circadian rhythmicity and insomnia, including the transient insomnia associated with transient and sustained operations. Experimental work on the possible adjustment of the circadian clock by melatonin is complicated by its sedative activity. This latter effect may improve sleep, thus alleviating the symptomatology of circadian desynchrony, and even normalising the sleep-wake cycle. Whether melatonin can induce a phase shift of circadian rhythms is an issue much debated [Arendt et al., 1997, Lewy and Sack, 1997, Sack and Lewy, 1997]. It may elicit a relatively weak phase shifting effect, but Czesler [1997] has emphasised that this may be insufficient to induce a reliable entrainment. Any such effect with melatonin needs to be established by physiological parameters other than sleep and wakefulness.

Although sedative activity of melatonin has been demonstrated, its usefulness as a hypnotic is not clear. Indeed, Roth and Richardson, 1997 have emphasised that the majority of studies have evaluated only a single dose, or a limited dose range, and that there is a need for unambiguous information on its activity related to dose and to time of administration. Further, dose response data using electroencephalography is essential to an adequate understanding of its activity. Daytime ingestion of melatonin would appear to lead to reductions in sleep latencies [Dollins et al., 1994, Nave et al., 1996, Reid et al., 1996, Hughes and Badia, 1997], but studies on its activity around the normal time of sleep have failed to establish a useful clinical effect, except possibly in elderly insomniacs [Monti et al., 1999, Hughes et al., 1998, Dawson et al., 1998].

However, the usefulness of a hypnotic in the management of sleep disturbance associated with continuous and intensive operations would be dependent on it being effective at all times of the circadian cycle. It is in this context that a dose response study on the activity of melatonin when given in the early and late evening in healthy volunteers was carried out. The activity of melatonin was studied on nocturnal sleep (23:00-07:30) and on evening sleep (18:00-24:00), using electroencephalography, and was compared with that of a benzodiazepine (temazepam 20 mg) which is often used by individuals coping with irregular patterns of rest in critical situations. [Stone et al., 2000]

The subjects were healthy male volunteers free of the use of medication. They gave informed consent to take part in the experiment that was approved by the local Ethics Committee. In the nocturnal experiment the subjects were eight males aged 20 to 30 (mean 23.4) years weighing between 63 and 100 (mean 77) kg, and in the evening experiment the subjects were six males

aged 21 to 31 (mean 26.5) years weighing between 69 and 89 (mean 77.3) kg. One subject participated in both experiments.

During the evening preceding the day of each experiment the subjects retired at their normal bedtime and consumed no more than two units of alcohol. In the experiment on nocturnal sleep, caffeinated beverages were avoided from midday, and in the experiment on early evening sleep, subjects abstained from caffeine throughout the day. The order of drug ingestion in both experiments was based upon a Latin Square design. Medication was identical in appearance and the experiments were double-blind.

Experiment I: Each subject reported to the laboratory on eight occasions, at intervals of at least one week, and ingested at 23:30, on separate occasions, melatonin (0.1, 0.5, 1.0, 5.0 and 10 mg), 20 mg temazepam (active control) and, on two occasions, placebo. An identical performance test session of 8-min duration was carried out before and after each sleep period (23:30-07:30).

Experiment II: Each subject reported to the laboratory on six occasions, at intervals of at least one week, and ingested at 18:00, on separate occasions, melatonin (0.5, 1.0, 5.0 and 10 mg), 20 mg temazepam (active control) and one placebo. A performance test session of 4 min duration was carried out after each sleep period (18:00-00:00).

Sleep and body temperature

Electroencephalography: The subjects slept in single light-proofed, sound attenuated and temperature controlled ($18 \pm 2^\circ\text{C}$) rooms. Standard techniques for recording and analysing sleep were used [Rechtschaffen and Kales, 1968]. Various measures were derived from the data for subsequent statistical analysis.

Subjective assessments: Subjective assessments of sleep were completed 15 min after rising. Subjects also estimated the time to sleep onset and the sleep duration. The Stanford Sleepiness Scale [Hoddes et al., 1973] was completed prior to and after each sleep period.

Performance

Subjects were well trained on all performance tasks and were observed during the tasks by means of closed circuit television. In the experiment on nocturnal sleep, tests were presented at 23:00 (0.5h before drug ingestion) and at 08:00 (8.5h after drug ingestion) in the following order: digit symbol substitution (DSS), letter memory recall, picture memory recall. During each session, mood and well being were assessed using a series of twelve 100 mm visual analogue scales [Nicholson et al., 1984]. In the experiment on early evening sleep, DSS only was measured at 00:30, i.e. 6.5h after drug ingestion.

Melatonin onset

Endogenous dim light melatonin onsets (DLMO) were determined on completion of the nocturnal sleep experiment. The subjects remained in constant dim light (< 8 lux) in an isolation unit from 17:00 to 03:00 and produced saliva samples at half hourly intervals. Salivary melatonin levels were determined by radioimmunoassay [English et al., 1993] and the dim light melatonin onset was calculated as the time at which melatonin levels reached twice the limit of detection of the assay (1.3 pg/ml). Immediately after providing each saliva sample, subjects were required to rate their fatigue level against 10 separate criteria on the Modified Samn-Perelli (MSP) checklist [Samn and Perelli, 1982]. From these ratings, a score in the range 0 (extremely fatigued) to 20 (extremely alert) was calculated.

Statistical analysis

An equation of the form: $\text{temperature} = a + b * \exp [c * \text{time}]$ was fitted to each subject's temperature data recorded during nocturnal sleep for each drug, and the values of a, b and c were estimated using a least squares fit. These three coefficients were analysed by ANOVA using a one factor model (drug) against subjects. A similar method was used for the temperature data recorded during early evening sleep, and the two coefficients (slope and intercept) were analysed

by ANOVA. The temperature data from both experiments, recorded at minute intervals, was meaned over 30 min intervals from lights out and analysed by ANOVA.

Night time sleep: One dose of melatonin (5 mg) reduced the duration of stage 3 in the first 100 min of sleep ($p < 0.05$), though analysis of mean values for melatonin failed to reveal any change with melatonin compared with placebo in any sleep measure. Temazepam increased stage 2 sleep (duration and percentage in the first 6h and over the whole night; $p < 0.01$), and duration in the first 100 min periods of sleep (from 59.1 min after placebo to 74.6 min after temazepam; $p < 0.05$) and third 100 min (from 53.8 min after placebo to 68.3 min after temazepam; $p < 0.01$). The latency to rapid eye movement (REM) sleep was also increased ($p < 0.05$) compared with placebo. With temazepam there was a reduction in total and percentage of stages 0 and 1 combined, both in the first 6h of sleep and over the whole night (compared with placebo and the mean of the melatonin doses $p < 0.01$).

Subjective measures: No difference was found between drug treatments in subjective assessments of sleep onset, sleep duration, sleep quality, alertness or mood. One subject reported vivid dreams and many awakenings with 0.5 mg melatonin, and sleep disturbance with early morning awakening with 1 mg melatonin. Another subject reported feeling "foggy" after 1 mg melatonin.

Temperature and performance: Body temperature during nocturnal sleep with 0.1 mg melatonin (36.18°C , $p < 0.05$) was lower than placebo (36.43°C) 6.5 to 7h after lights out, but no other changes in body temperature with melatonin, either related to dose or time, were detected. With temazepam, body temperature during nocturnal sleep was reduced 4.5 to 5h (36.12°C , $p < 0.05$), 5 to 5.5h (36.11°C , $p < 0.01$), 5.5 to 6h (36.14°C , $p < 0.01$), 6 to 6.5h (36.18°C , $p < 0.05$) after lights out, compared with placebo (36.35 , 36.38 , 36.43 , 36.43°C , respectively). There were no changes in performance after the nocturnal and early evening sleep periods with melatonin or temazepam.

Melatonin onset: The endogenous dim light melatonin onset of all eight subjects occurred between 20:40 and 23:15. The mean time of melatonin onset was 22:02. Mild fatigue was reported on the Sam-Perelli fatigue checklist from 21:30h.

Early evening sleep

Objective measures: Melatonin increased total sleep time, sleep efficiency, the total duration of stage 2 sleep ($p < 0.001$, all doses), the duration of stage 2 sleep in the second (0.5 mg, $p < 0.01$; 1 mg, $p < 0.05$; 10 mg, $p < 0.001$) and third (0.5, 5 and 10 mg, $p < 0.001$; 1 mg, $p < 0.05$) 100 min interval of sleep. It also increased the percentage of stage 2 sleep (two lower doses, $p < 0.01$; 5 mg, $p < 0.05$; 10 mg $p < 0.001$). Melatonin increased the number of REM periods (0.5 mg, $p < 0.05$; 1 to 10 mg, $p < 0.001$), the duration of REM sleep in the third 100 min interval of sleep (1 mg, $p < 0.05$), increased the number of stage shifts (0.5 mg, $p < 0.05$; 10 mg, $p < 0.01$), and the percentage of wakefulness ($p < 0.05$, all doses). Melatonin (5 mg) increased the duration of stage 3 sleep (16.3 min) in the second 100 min interval of sleep, compared with placebo (4.7 min; $p < 0.05$), and increased the total duration of stage 1 sleep and the duration of stage 1 sleep in the second 100 min interval of sleep ($p < 0.05$). Melatonin (10 mg) increased wakefulness in the first 100 min interval of sleep, compared with temazepam ($p < 0.01$).

Temazepam (20 mg) increased total sleep time and sleep efficiency ($p < 0.001$). It also increased the number of stage shifts ($p < 0.05$), reduced wakefulness (total duration, $p < 0.05$ and percentage, $p < 0.001$), increased stage 2 sleep (total duration, percentage, and duration in the third 100 min of sleep, $p < 0.001$) and increased the duration of slow wave sleep ($p < 0.05$).

Subjective measures: Melatonin, improved subjective sleep quality (0.5 to 5 mg doses, $p < 0.001$; 10 mg, $p < 0.01$) and reduced alertness following sleep (0.5 and 5 mg doses, $p < 0.01$; 1 and 10 mg doses, $p < 0.05$). The two lower doses of melatonin also increased the subjects' perceived requirement for sleep after the sleep period (0.5 mg, $p < 0.05$, 1 mg, $p < 0.01$). Temazepam (20 mg) reduced sleep onset latency ($p < 0.05$), improved sleep quality ($p < 0.001$), and reduced alertness following sleep ($p < 0.001$). Subjects reported that sleep quality was better after temazepam than melatonin ($p < 0.05$ compared with 0.5, 1, 5 mg; $p < 0.01$ compared with 10 mg melatonin).

Temperature and Performance: No effects were observed with melatonin or temazepam on body temperature during early evening sleep, and there were no changes in performance after the sleep period with either drug.

In the present study on healthy volunteers using electroencephalography we have been unable to establish a consistent effect of melatonin on nocturnal sleep across the dose range 0.1 to 10.0 mg. The only change observed was that 5-mg led to a reduction in stage 3 in the first 100 min of sleep. A reduction in stage 3 and 4 sleep with 5 mg melatonin has been reported previously in studies on a simulated 9h phase advance [Stone et al., 1996], but it is considered that this minimal effect observed in the present study has little, if any, clinical significance. In contrast, the active control, temazepam (20 mg), had beneficial effects on various sleep parameters including reduced wakefulness and drowsy (stage 1) sleep and increased stage 2 sleep.

On the other hand, we were able to establish an unequivocal effect of melatonin on early evening sleep across the dose range 0.5 to 10.0 mg. The effect was fully developed with the 0.5 mg dose, with no additional effect observed above this dose. The increase in the number of REM periods observed during the early evening sleep was most likely due to an increase in total sleep time, as there was no change in the REM/non-REM ratio. Overall, the effect of melatonin was similar to that of 20 mg temazepam.

These studies suggest that melatonin is unlikely to possess useful hypnotic activity in healthy individuals when administered around the normal time of sleep, though the effect of melatonin on early evening, as opposed to nocturnal sleep, is comparable with that of a low dose of a benzodiazepine. Clearly, time of administration would appear to be a crucial factor in the appearance of the hypnotic activity of melatonin. In humans melatonin secretion occurs in the late evening [Tzischinsky et al., 1993], as was observed in the present experiment on nocturnal sleep. It is, therefore, possible that in healthy young adults the limited hypnotic activity of melatonin is fully developed with the normal nocturnal endogenous secretion and that raising the plasma level of melatonin, at that time, by ingesting melatonin, may have little, if any, further effect. On the other hand, daytime doses, which raise plasma melatonin levels to within or beyond the normal, nocturnal range, improve sleep [Dollins et al., Nave et al., 1996, Reid et al., 1996, Hughes and Badia, 1997, Zhadanova et al., 1995, Nave et al., 1995]. This time-of-day dependent response, together with the absence of a dose response over the range 0.5 to 10.0 mg, suggests that the effect of melatonin is fully developed at the natural endogenous plasma level.

The hypnotic activity of melatonin observed after administration in the early evening was not accompanied by a change in core temperature [Chan 1999]. In this way our results support the view of Nave et al [1995] and Tzischinsky and Lavie [1994] that the activity of melatonin is likely to be due to a direct effect on sleep rather than to any secondary effect of a fall in temperature. However, though other authors have reported changes in core temperature, [Reid et al., 1996, Hughes and Badia, 1997, Lushington et al., 1997, Gilbert et al., 1999], Nave et al [1998] have suggested that any hypothermic effect of melatonin occurs after the onset of hypnotic activity.

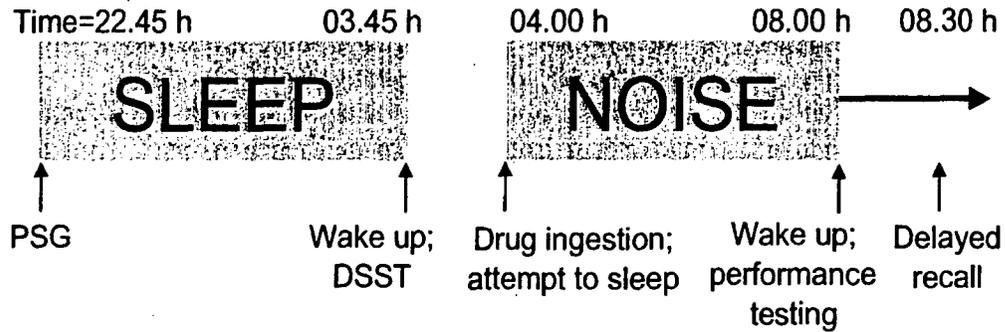
The present study has demonstrated that the hypnotic effect of melatonin is time-of-day dependent, and this, together with evidence that the ingestion of melatonin in certain circumstances may lead to sleep disruption [Middleton et al., 1996], suggests that melatonin is only likely to be useful as a hypnotic at certain times of the circadian cycle which have yet to be delineated. This raises the issue of a 'window of effect' but it is unlikely that any individual coping with sustained and continuous operations would possess sufficient information on their circadian rhythm of melatonin secretion to ensure ingestion of the compound at times to avoid sleep disruption and to ensure some beneficial effect on sleep. On the other hand, whether individuals coping with time zone changes can use melatonin for entrainment remains controversial, and the present study does not provide any input for the debate on the phase shifting properties of melatonin.

ZALEPLON

While benzodiazepines such as temazepam and related drugs such as zolpidem are suitable for use as sleep inducers in sustained and continuous operations, these drugs are only suitable if at least six hours intervenes between ingestion and the requirement to be alert. When shorter periods are available for sleep drugs such as temazepam are not suitable as their use would be associated with impaired performance. In addition there may be a requirement for middle of the night administration when sleep is disturbed by intrinsic or extrinsic factors.

For the treatment of middle of the night insomnia caused by an intrinsic condition in the individual or by environmental factors such as noise it is necessary to move to the most rapidly eliminated hypnotic recently introduced into clinical practice, zaleplon (Sonata[®]), a pyrazolopyrimidine compound that binds selectively to the γ -aminobutyric acid (GABA)_A receptor complex [Beer et al. 1997.; Dämgen and Lüddens, 1999]. It is rapidly absorbed, with peak plasma concentrations at around 1h, and rapidly eliminated with a plasma elimination half-life of approximately 1h [Beer, Ieni AJR, Wu WH, et al, Hurst M and Noble S]. Zaleplon therefore has a rapid onset of action and a rapid elimination half-life and this profile is unlike any other hypnotic drug in the market today. The structure of zaleplon is unrelated to barbiturates, benzodiazepines and other hypnotic drugs. It also possesses agonist properties and it lacks many of the side effects commonly associated with other hypnotic drugs due to its short duration of action. It has been shown to have useful hypnotic effects in patients with insomnia [Dietrich and Farr 1995, Walsh et al 1998, 2000a, 2000b, 2000c, Ancoli-Israel et al 1999, Elie et al., 1999, Cluydts 2000, Drake et al 2000,], these effects included reduction in sleep onset latency and this was not associated with rebound insomnia on withdrawal or with any other withdrawal symptoms. In addition there was no tolerance during therapy reported. In this way zaleplon can be used as a treatment for those patients with sleep onset insomnia or indeed for those with situational insomnia which manifests itself with problems falling asleep. Thus zaleplon may prove to be an extremely useful drug in the treatment of insomnia associated with circadian rhythm disturbance such as jet lag or when required to work at night and sleep during the day. Its rapid onset and swift duration of action would suggest its use to aid sleep after eastward travel where it is necessary to fall asleep at a time when the circadian rhythm is at its alert phase. In those who are required to retire to bed earlier in order to anticipate an early start it may also help with problems falling asleep. However, many other short acting hypnotics may be useful in these circumstances although the lack of rebound insomnia with zaleplon may make it more suitable in those who carry out skilled work. The unique property of zaleplon is its ability to promote sleep in the middle of the night without any residual effects on performance on the following morning [Vermeeren et al 1998, Danjou et al 1999, Walsh et al 2000, Stone et al 2000, Volkerts et al 2000, Zammit 2000,]. The subjects were healthy volunteers with situational middle-of-the-night insomnia, rather than patients with sleep maintenance insomnia, as in the previous study, which can be inconsistent in an experimental context [Walsh JK et al, 2000] In a study carried out in the United Kingdom situational insomnia was induced using a sound stimulus, a method that has been used previously to investigate the hypnotic properties of benzodiazepines and the hormone melatonin [Saletu et al 1985, Saletu et al 1987, Waldhauser et al 1990, Gieschke et al 1994, Cluydts et al 1995, Terzano et al 1995, Parrino et al 1997]. Since the sound stimulus used in these previous studies (traffic noise or continuous white noise) disturbed sleep, but did not prolong sleep latency *per se*, a pure tone pulse, as this has been shown to increase sleep latency [Nakagawa 1987].

LPS and Performance in Noisy Environment



Noise = 80 db(A) 1 khz pure tone pulse of 50 sec duration with an intertone interval of 1 sec. Turned off after 10 min of persistent sleep or 2 h without sleep.

Zopiclone was used as an active control to indicate the sensitivity of the experimental procedures. It is an established hypnotic with an elimination half-life of around 5-h, and would be expected to have residual effects on performance 4 h after administration [Nicholson, 1998]. Thirteen healthy volunteers were studied. Before the study, an adaptation night in a single room was undertaken to familiarise each subject with the recording procedures and to establish whether their sleep patterns were normal. At least four days after the adaptation night, the subjects reported to the laboratory on two occasions separated by at least one night to establish whether they were sensitive to the sleep-disrupting effects of noise. On both of these occasions, after a 5 h sleep period (22:45-03:45) in a quiet environment, the subjects got up and completed a 4-min test of performance (the digit symbol substitution task). They returned to bed at 04:00 and, after ingestion of placebo (administered single blind), they were asked to fall asleep. On the first single-blind placebo night, there was no sound stimulus (the mean background noise level in the bedrooms was 36.8 dB [A], while on the second single-blind placebo night the subjects were exposed to a pure tone pulse described below). The sound stimulus was started at 04:00 and a recordist monitored the electroencephalogram and determined the latency to persistent sleep (10 min of stage 2, 3, 4, or rapid eye movement (REM) sleep, methods described below). The sound stimulus was stopped either after persistent sleep had been reached, or after 2 h if the subject did not fall asleep. At 08:00, 4 h after drug ingestion, the subjects were awoken, if necessary, and they completed a battery of performance tasks and assessments of well being (described below). Only those subjects who had an increase of at least 10 min in the latency to persistent sleep (LPS) from the night without noise to the night with noise were included in the double-blind phase of the study. They subsequently reported to the laboratory on four occasions separated by a period of at least four nights. The experimental procedure was identical to the second single-blind placebo night, except that at 04:00, each subject was administered placebo, zaleplon 10 mg, zaleplon 20 mg, or zopiclone 7.5 mg, double-blind, on separate occasions according to a four-period randomised cross-over design.

Sound stimulus

The sound stimulus was an 80 dB[A] 1kHz pure tone pulse with an inter-tone interval of 1 s, rise-decay times of 2.5 ms, and a duration of 50 ms. The sound stimulus was recorded onto a computer and replayed simultaneously into each bedroom via loudspeakers positioned 1 m behind the subject's head. Before each test night, a sound level meter was positioned at the subject's pillow in each bedroom and used to ensure that intended noise levels were replayed and that noise doses did not exceed those permitted by UK Health and Safety legislation.

Psychomotor performance and memory tests

Subjects were trained to plateau performance on all tests before the study began and were observed during the tasks by means of closed circuit television. The tests were presented in the following order: digit symbol substitution, immediate word recall, critical flicker fusion, choice reaction time and delayed word recall.

Electroencephalography

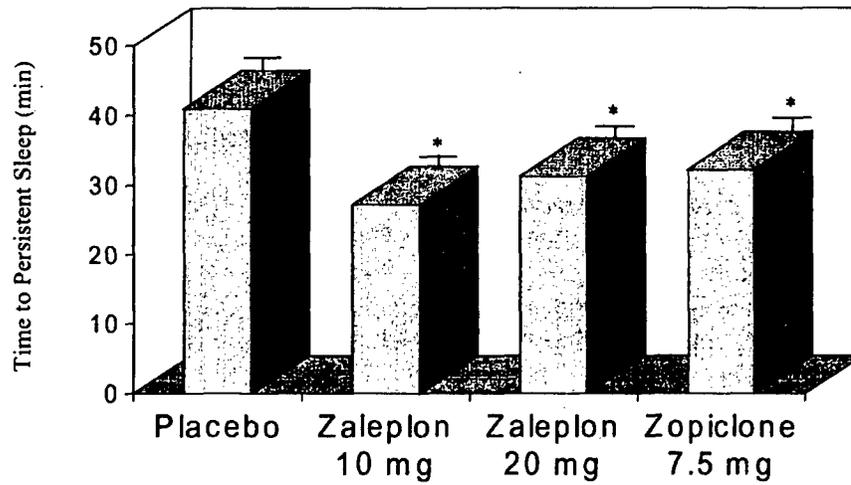
The subjects slept in single light-proofed, sound-attenuated, and air-conditioned rooms. Silver-silver chloride electrodes were used to record electroencephalograph (EEG) activity from the O₁-A₂ and C₄-A₁ positions, together with bilateral electro-oculograms (EOG) and the submental electromyogram (EMG), on a Nicolet Biomedical Ultrasom (digital EEG) system via three Nihon-Koden 4300 series EEG machines. A simulated paper speed of 10 mm/sec was used and each recording from the second period of sleep (04:00 to 08:00) was scored manually upon completion of the study into 30s epochs according to the criteria of Rechtschaffen and Kales [21]. Various measures were derived from the data for subsequent statistical analysis.

Statistical methods

The sample size estimate was based on an estimate for the DSST of the standard deviation (6.78 symbols) of the difference between zaleplon 10 mg and placebo in a previous study [8]. The power calculation indicated that 12 subjects would be required to detect a difference of 6.1 symbols in the DSST with 80% power at the 5% significance level.

The data were analysed by an analysis of variance (ANOVA) with subjects, period, treatment, and first order carry-over as factors in the model. First order carry-over was not significant, and was therefore removed from the ANOVAs and least squares means calculated. A Bonferroni adjustment was made for the three active treatments compared with placebo. The 5%, 1% and 0.1% significance levels adjusted for multiple comparisons were: $p < 0.0167$ (0.05/3); $p < 0.0033$ (0.01/3); and $p < 0.0003$ (0.001/3), respectively.

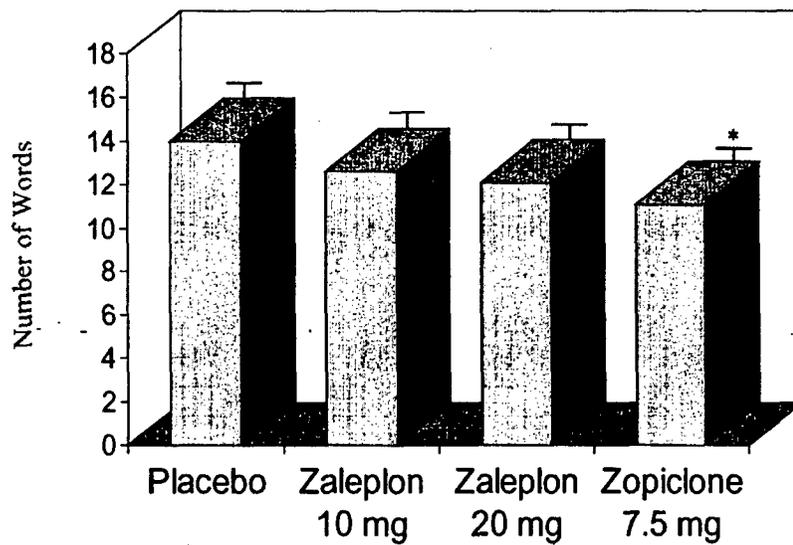
Latency to Persistent Sleep



* $P < 0.05$

Figure 3

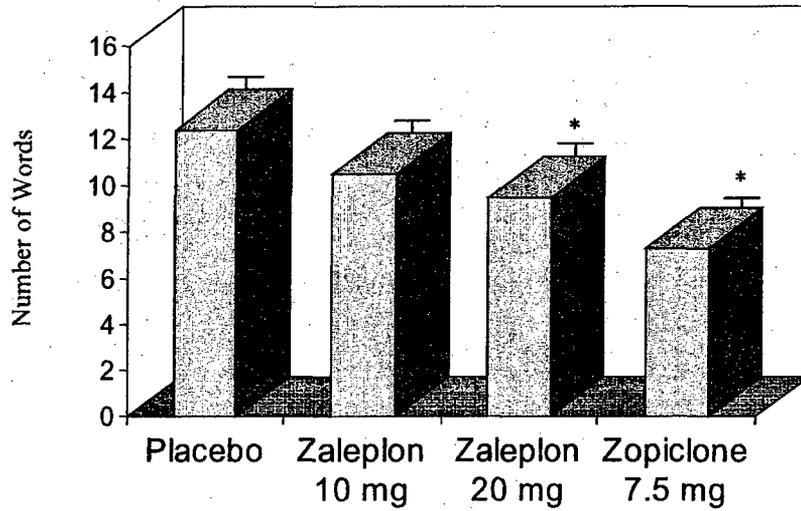
Word Learning Test: Immediate Recall 4 hours post dose



* $P < 0.05$

Figure 4

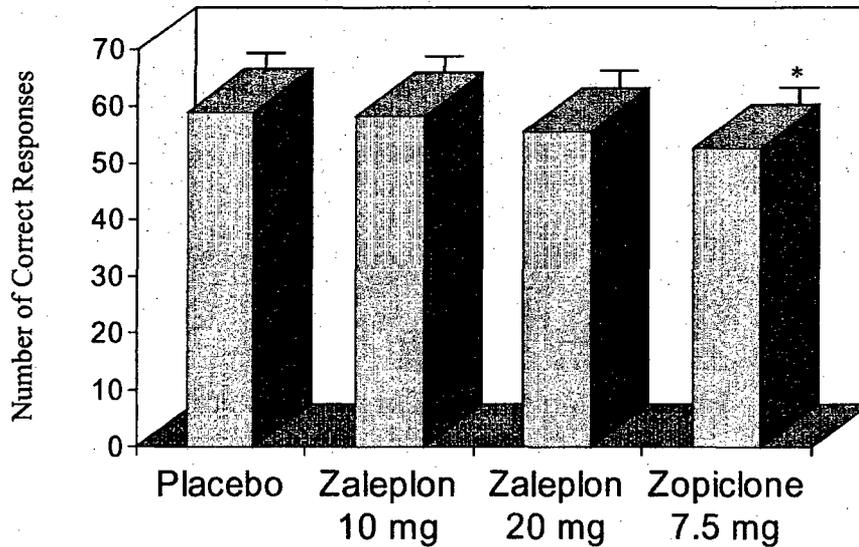
Word Learning Test: Delayed Word Recall 4.5 hours post dose



* $P < 0.05$

Figure 5

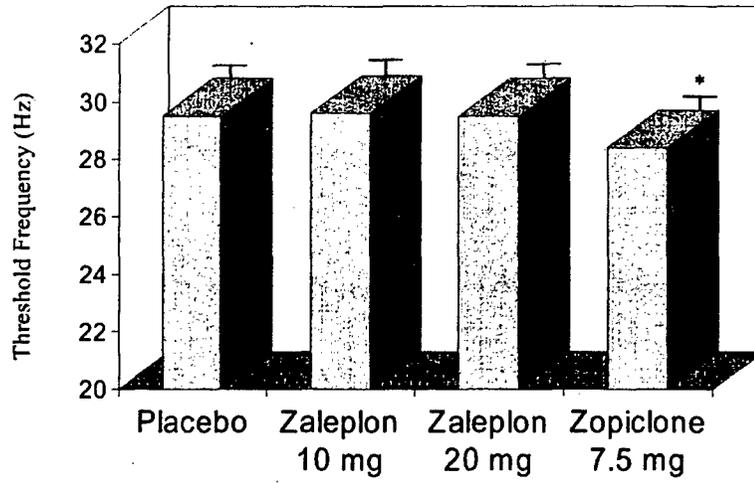
Digit Symbol Substitution Test 4 hours post dose



* $P < 0.05$

Figure 6

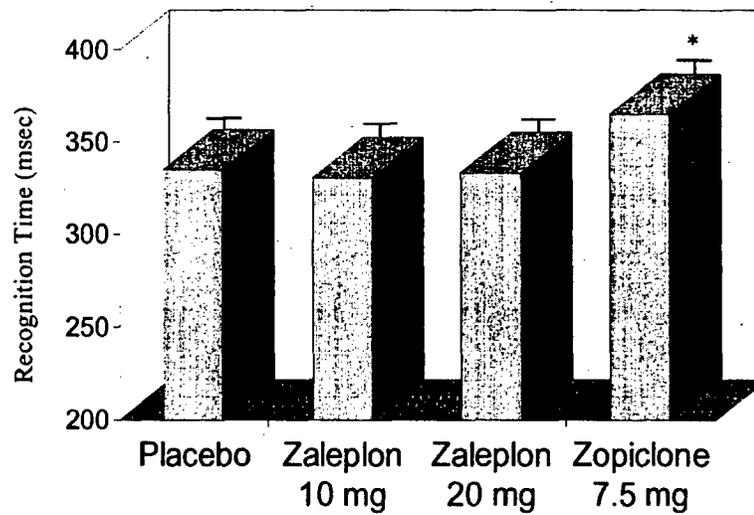
Critical Flicker Fusion 4 hours post dose



* $P < 0.05$

Figure 7

Choice Reaction Time Recognition 4 hours post dose



* $P < 0.05$

Figure 8

Results

One subject was withdrawn from the study after the third drug treatment because drug treatments two and three had been administered in reverse order and therefore the order of treatment did not meet that specified by the randomisation.

No residual effects of zaleplon (10 and 20 mg) were found on psychomotor performance, memory, or subjectively assessed sedation. The active control, zopiclone (7.5 mg), impaired performance 4 h after ingestion on the digit symbol substitution task ($p=0.004$) and choice reaction time task ($p=0.001$), and reduced the number of words recalled on the delayed memory recall task ($p=0.001$), compared with placebo (Table I). However, the subjects as a group did not report any change in sedation 4-h after zopiclone ingestion, compared with placebo.

The latency to persistent sleep was reduced by both doses of zaleplon (10 mg, $p=0.001$; 20 mg, $p=0.014$) and the duration of stage 1 (drowsy) sleep was reduced by the 20 mg dose ($p=0.012$), compared with placebo (Table II). Zopiclone reduced stage 1 sleep ($p=0.001$), increased stage 3 sleep ($p=0.0001$) and increased total sleep time ($p=0.003$), compared with placebo.

No serious adverse events or discontinuations due to adverse events were reported during the study. The only treatment-emergent adverse event that was reported by more than one subject was a bitter after-taste with zopiclone ($n=5$ subjects, 38%).

Zaleplon appears to be a useful hypnotic for individuals who experience difficulty in falling asleep either at bedtime or in the middle of the night, as it is free from residual effects 4h after ingestion. Such sleep problems may be common as a sleep survey in the United States found that 56% of respondents reported difficulty in falling asleep and 67% reported awakening in the middle of the night [Ancoli-Israel and Roth, 1999]. Many currently available hypnotics will sustain sleep and reduce the incidence of early morning awakenings if taken at bedtime. Given that the severity of an individual's sleep problem is likely to vary from night to night, a potential benefit of zaleplon may be a reduction in the requirement for nightly prophylactic use of hypnotic medication. This may avoid the phenomenon of rebound insomnia after cessation of prolonged treatment. Clearly, assessment of the nature of the insomnia would be essential and patients would need to be given guidelines on the use of such a short-acting hypnotic in order to avoid ingestion of unnecessarily large prophylactic doses in an attempt to sustain sleep.

Little information is currently available on the effectiveness of zaleplon in healthy volunteers with transient insomnia. The present study suggests that the drug is likely to be useful following a westward time zone change when individuals may experience an early morning awakening and are unable to return to sleep. Zaleplon may also be effective if used occasionally to promote sleep in those who have to rest at unusual times of the day, for example, in the early evening before a night shift or for naps during military operations. However, further work would be required to establish whether zaleplon is useful in the management of this type of transient insomnia in healthy individuals involved in skilled activity when residual effects are to be avoided.

In conclusion, the present study has shown that zaleplon (10 mg and 20 mg) is free from residual effects 4h after ingestion in the middle of the night, and possesses hypnotic properties in a noise-induced sleep maintenance insomnia model in healthy subjects.

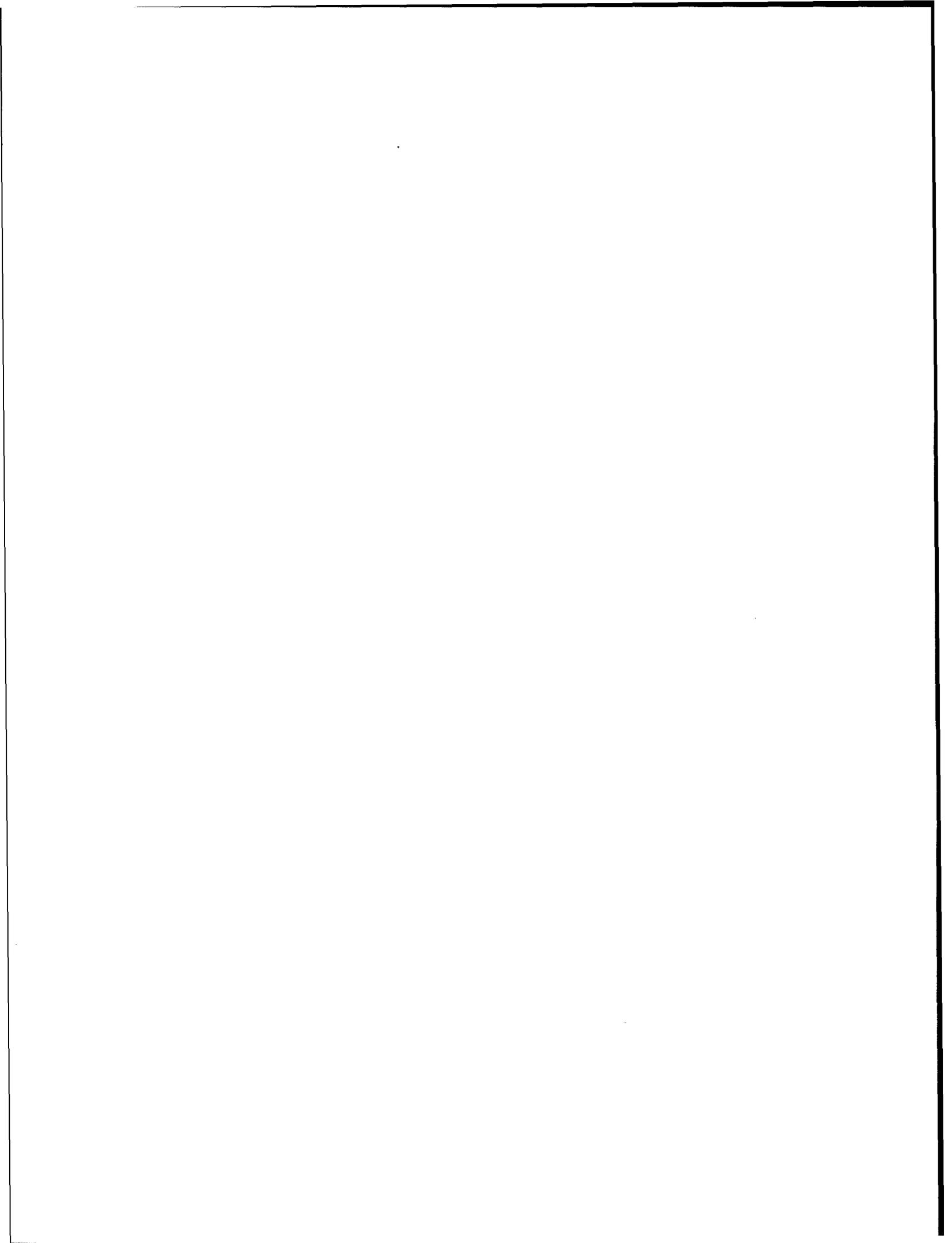
CONCLUSION

As far as sustained and continuous military operations are concerned the hypnotic temazepam remains the drug of choice for ensuring sleep during rest periods of six hours or more. Melatonin analogues may prove to be useful in the future. Further studies on the use of zaleplon for short sleep periods during an irregular work/rest schedule are in progress.

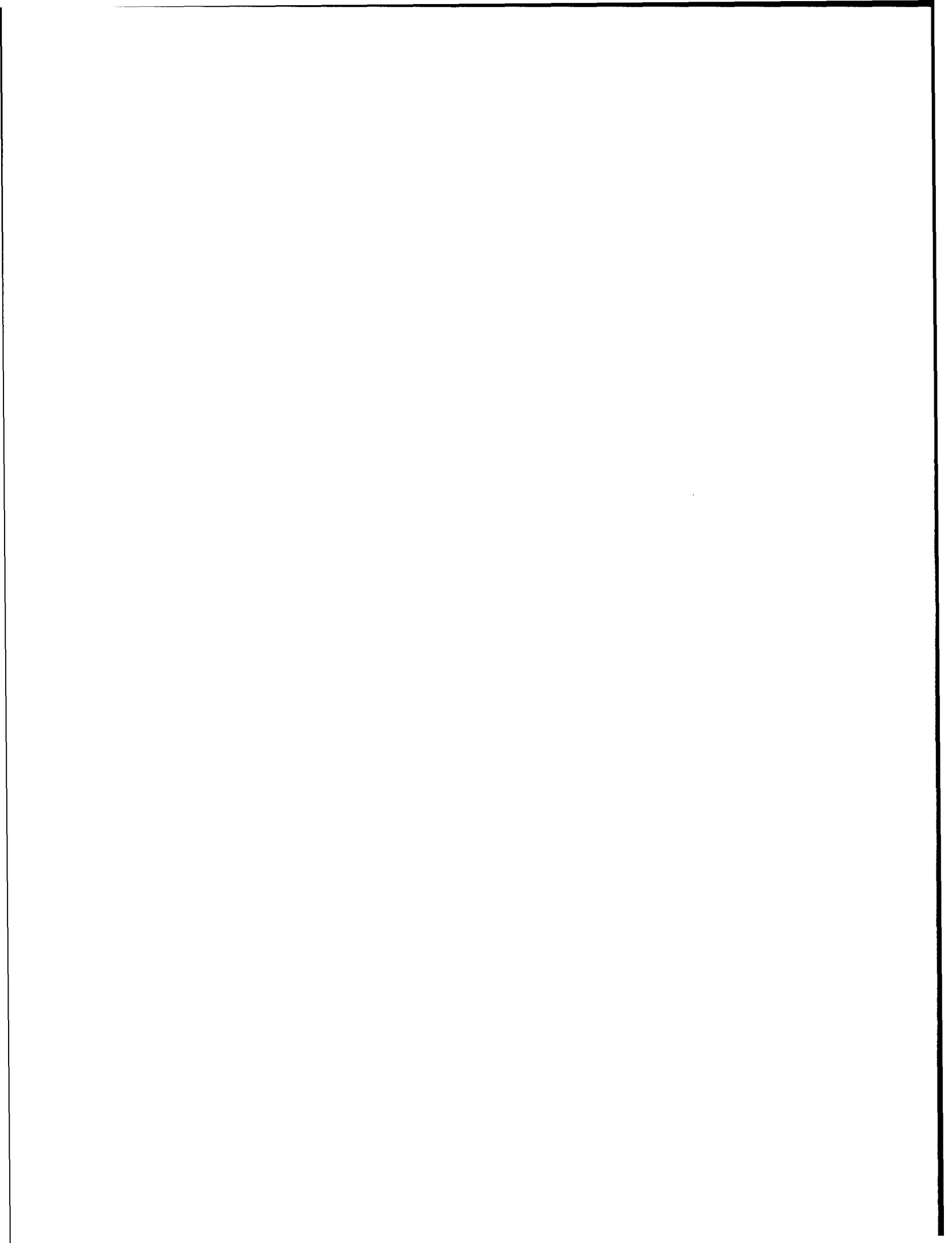
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