Caffeine or melatonin effects on sleep and sleepiness
after rapid eastward transmeridian travel

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Running head: slow release caffeine or melatonin and recovery after jet-lag

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Abstract

We measured the effects of slow-release caffeine (SRC) and melatonin (MLT) on sleep and daytime sleepiness after a 7-time zone eastbound flight. In a double-blind, randomized, placebo-controlled study, each of 3 groups of 9 subjects was given either 300 mg SRC on Day1-Day5 (D1-D5) (08:00) or 5 mg MLT from D1 (17:00) and D0 (16:00) to D3 (23:00), or placebo (PBO) at the same times. Nighttime sleep was evaluated by polysomnography and daytime sleepiness, from measurements of sleep latencies and continuous wrist actigraphy. Compared to baseline, we found a significant rebound of Slow Wave Sleep (SWS) on Night1-Night2 (N1-N2) under PBO and MLT, and a significant decrease in Rapid Eye Movement (REM) sleep on N1 (PBO) and N1-N3 (MLT). Sleepiness was objectively increased under PBO (D1-D6) and MLT (D1-D3). SRC reduced sleepiness but also tended to affect sleep quality until the last drug day. In conclusion, both drugs have positive effects on some jet-lag symptoms following an eastbound flight: SRC on daytime sleepiness and MLT on sleep.

Key words: Recovery after jet-lag, sleep architecture, sleepiness, slow release caffeine, melatonin
INTRODUCTION

Rapid travel by air across multiple time zones exposes the traveler to the phenomenon of jet lag, which is characterized by sleep disturbances, daytime sleepiness and impaired performance (34). These disturbances may be alleviated by pharmacological aids such as short-acting hypnotic drugs to induce sleep during the flight and thereby to reduce fatigue after landing (29). However, such drugs are not without adverse effects (23, 31). Melatonin, a pineal gland hormone, is thought to speed up recovery after jet-lag (2, 3), although its side effects have yet to be characterized. A new slow-release formulation of caffeine (SRC) has been found to maintain vigilance and performance during a 32-h sleep loss with no side effects at a dosage of 300 mg twice a day, and without modification of sleep during the recovery period (17). A single 600-mg dose of SRC administered between 20:00 and 21:00 h has been shown to alleviate the deleterious effect of sleep deprivation for at least 24 h (24). Indeed, with SRC the plasma plateau of caffeine is attained within approximately 4 h and this level can be maintained for 4-6 h without overshooting the unwanted-effect threshold (Fig. 1) (6). Furthermore, it could be suggested a possible role of caffeine on circadian rhythmicity by acting on A2b adenosine receptors of the pineal gland (36). We hypothesized that melatonin and slow release caffeine could respectively improve sleep and mitigate daytime sleepiness following transmeridian flights. The aim of our study was to compare the effects of SRC with those of MLT on recovery sleep and daytime sleepiness after a 7-time zone eastbound flight, using subjective and objective methods. This work was part of a large real-world French-American study called "Operation Pegasus" in which around 140 physiological, psychological and biological parameters were measured (18, 25).
METHODS

Subjects

This double blind, randomized, placebo-controlled study was conducted on 27 healthy volunteers from a US Air Force Reserve Unit that was representative of the US population (18 males and 9 females; 15 Caucasians, 9 Hispanics and 3 Afro-Americans; age: 35.3 ± 8.1 yr. (age range: 19-47 yr.); weight: 77.6 ± 15.8 kg; height: 170 ± 10 cm). They underwent a medical evaluation before participation, including biological sampling and EEG. They also were examined by a psychiatrist and a specialist of sleep who found no history of psychiatric or sleep disorders for all subjects. Horne and Östberg's questionnaires showed that they were neither morning nor evening types (16); they habitually went to bed between 23:00 and 24:00 h and woke up between 06:00 and 07:00 h with a sleep duration ranging from 6.5 to 7.5 hours. They had not experienced a transmeridian flight in the two months before their enrollment in this study. They were non-smokers and did not consume large amounts of xanthine-based beverages on a regular basis (coffee, tea and cola: equivalent to less than 3 cups a day), nor had they taken psychotropic drugs or melatonin in the three months prior to the study. They abstained from drinking alcohol or caffeine-containing beverages during the experiment; this commitment was strictly controlled by the experimenters. They gave informed written consent prior to participation. In accordance with the 1964 declaration of Helsinki, the experimental protocol was approved by the Human Ethics Committees of the Robert Ballanger Hospital, Aulnay sous Bois, France.

Experimental protocol (Fig. 2)

The subjects were housed and trained at Brooks AFB in San Antonio, Texas, USA over six days and their routines were identical. During the first five days, they were familiarized with the procedures and the experimental tests and measurements, including the nocturnal EEG. Baseline data were obtained during the last night and day (N-1, D-1) to avoid the first night
effect (1). The flight was scheduled on D0, 15:00 (US time) for a 7-time zone eastbound flight to Mont de Marsan, France. According to the test protocol, the subjects were prohibited from sleeping during the flight so that they remained awake 33 hours from last awakening at Brooks AFB to first sleep in France. During the flight, they played cards or read and had to complete sleep logs and questionnaires at regular intervals; their state of wakefulness was checked subjectively by the experimenters. The arrival was on D1, 6:00 (French time) and recovery lasted 10 days (D1-D10) and 9 nights (N1-N9). Before and after the flight, the subjects were required to follow the same daily routine: wake up at 7:00 (beginning of light exposure), breakfast at 8:00, morning tests between 9:00 and 12:00, lunch between 12:30 and 13:30, evening tests between 14:00 and 17:00, light muscular activity (walking in the woods) between 17:30 and 18:30, dinner at 19:30, fitting of EEG electrodes from 20:00, leisure (reading, games) until bedtime at 23:00 (lights off). During the morning (9:00-12:00) and afternoon (14:00-17:00) test periods, when not napping, subjects followed a rigorous course of activities involving cognitive and physical performance testing (18). The subjects were confined to their rooms each evening and the dormitories were frequently patrolled by the investigators; they were restricted to a narrow area on base and never away from supervision during the day. Normal daylight nighttime darkness conditions were the same for all subjects throughout the experiment to avoid any bias related to a shift in circadian rhythms. None of the subjects has slept, eaten, drank or performed uncontrolled physical activity outside the authorized periods.

The 27 subjects were allocated randomly into three parallel groups, each containing 3 women and 6 men, to be administered either 300-mg slow release caffeine (SRC), 5-mg melatonin (MLT) or a placebo (PBO). 300-mg SRC was administered from D1 to D5 at 8:00, 5-mg synthetic MLT on D0 (16:00), D1 (17:00) and from D1 to D3 (23:00), and PBO in the same schedule (Fig. 2). The MLT intake schedule corresponded, before, during and after the flight, to bedtime in France. MLT with a degree of purity of 100% (measured by HPLC) was provided by Helsinn Chemicals SA (via Industria, Biasca, Switzerland) and SRC and PBO (lactose) by Nestec Research Center (Lausanne, Switzerland). The pharmacokinetics of SRC
is shown on Fig. 1. MLT, SRC and PBO were conditioned in capsules by Nestec according to standard double-blind procedures.

Measurements

Sleep

Baseline and recovery sleep architecture was assessed from standard polysomnographic recordings including electroencephalography (C3/Cz, O1/O2, referenced to an A1 ground electrode on the mastoid apophysis), electrooculography of each eye (oblique and horizontal derivations), chin electromyography. Polysomnography electric signals were recorded using TEAC recorders (Tekelec France, Sèvres, France) then sampled, amplified and stored using a portable Medilog 9000-2 (Oxford Medical Instruments, Abingdon, England) from 23:00 to 07:00 during the baseline (N1) and recovery (N1-N9) nights (Fig 2). EEG recordings were scored in 30-s epochs according to standard criteria (26) by a researcher who was unaware of the medication taken (SRC, MLT or placebo). We calculated for each night: sleep period time (SPT: time from falling asleep to last awakening), total sleep time (TST: difference between SPT and wakefulness after sleep onset (WASO)), sleep efficiency index (SEI: TST/TIB, with TIB: time in bed) and sleep onset latency (SOL: time from lights out to 1st episode of stage 2). We also measured SWS and REM sleep latencies (time from 1st stage 2 to 1st epochs of stage 3 and REM sleep, respectively). Each stage of sleep was analyzed by measuring total duration and percent of TST; the number of SWS and REM sleep episodes were also counted. For this long (about 2 weeks) field study, sticking electrodes on the skull using collodion would have been risky (risk of skin abrasion) and would have taken too much time. Therefore, we used caps on which the electrodes were inserted (electrocap, Vickers Medical France, Marne la Vallée, France) and after the cap was slipped on the head, conductive paste was injected through each electrode. For reasons of convenience (feeling of discomfort and request for shampooing before bedtime, what was impossible), some women refused to wear the cap during every night. Moreover, we knew, for having used this device in a previous
study (17), that in our longhaired female subjects, electric signals would have been likely to be lost or of a poor quality. We were unable to check directly the quality of the signals. For these reasons, a too small sized female population would have been recorded in good conditions and in order to maintain our group of subjects as homogeneous as possible, we decided to discard all our female subjects from the polysomnography. However, qualitative and quantitative aspects of sleep were evaluated in male and female subjects from sleep logs completed after wake-up from D1 to D10, as used previously (33). Sleep log questions were about bed and wake time, sleep latency (<15 min, 15-30 min, 30-45 min, > 45 min), awakenings and sleep periods (noted by on a 24-h scale with a precision of 15 min), sleep quality (light, intermediate, deep), dreams quality (pleasant, unpleasant), wake up quality (very easy to very difficult), and finally, subjective aspect of sleep duration (sufficient or not).

Daytime sleepiness

Over baseline and recovery periods, sleepiness was assessed in all subjects from EEG recordings by sleep latencies tests (SLT), assuming that sleepiness is a physiological need state that leads to an increased tendency to fall asleep (10). However, our method was not a standardized Multiple Sleep Latencies Test (MSLT) (10) because sleep latencies were measured with only 2 naps (at 9:00 and 14:00). Like for a MSLT, subjects were instructed to allow themselves to fall asleep or not to resist falling asleep while lying with eyes shut in a quiet, dark room. The recordings were stopped if subjects did not fall asleep within 20 min after the start of the test period (lights off) or after either three consecutive 30-s epochs of stage 1 or one first 30-s epoch of stage 2 sleep or of REM sleep.

Continuous wrist actigraphy was also employed to evaluate sleepiness objectively (21, 22, 27). Subjects wore a piezoelectric accelerometer (Gaehwiler Electronic, sensitivity: 0.1 G, sampling rate: 8 Hz, band-pass filter: 0.25-3 Hz, data acquisition period: 15 s) on their non-dominant wrist throughout the experiment. The number of movements with a force greater than 0.1 G was counted, then was averaged over the following periods: 7:00-9:00, 9:00-12:00
(morning test period), 12:00-14:00, 14:00-17:00 (afternoon test period), 17:00-19:00, 19:00-23:00, 23:00-03:00 and 03:00-07:00.

Sleepiness was subjectively evaluated by the “sleepy-awake” item from the Bond and Lader's visual analog scales (VAS) (7) during baseline and recovery periods, and also during the flight, 1, 3, and 5 hours following drug intake (16:00).

 Except continuous actigraphy, these objective and subjective measurements were taken at 9:00 and 14:00 corresponding to the hyper and hypovigilance periods defined by Lavie (19).

**Oral temperature**

In order to check the synchronization of our subjects before the flight in the USA and their resynchronization in France as well, oral temperature was measured at 2-h intervals between 7:00 (wake up) and 23:00 (bedtime), using an electronic thermometer.

Statistical analysis

Sleep and sleepiness data were analyzed separately and compared by two-way ANOVA (drug: SRC, MLT, placebo; period of time: recovery vs baseline) with repeated measurements over time. The level of significance (p) was set at 0.05. In case of interaction between drug and time (night or day), drug and time effects were analyzed respectively across time and for each treatment, using a Newman-Keuls test.
RESULTS

Sleep architecture

Baseline sleep

Since analysis of the baseline polysomnographic recordings did not reveal any first night effect, the subjects were allocated at random into three groups (SRC, MLT and placebo, see methods). There were no significant differences in sleep parameters between the subjects of these three groups (Table 1).

Recovery sleep (table 1)

Comparing data measured during recovery from SD within each drug group, no subject slept longer than on baseline night (N-1). TST, SPT and WASO did not change significantly throughout the experiment in all groups, except SPT which fell by ~30 min in the SRC group on N4 (p < 0.05). However, compared to baseline, SRC subjects increased their WASO by about 40 and 20 min on N3 and N4, then dropped about 40 min in N5, although these changes did not reach significance. Since TST and TIB were constant for all subjects, SEI did not vary throughout recovery in any of the groups.

Compared to baseline, sleep latency, non-REM and REM sleep measured during recovery depended on treatment.

- For sleep latency (SOL, Fig. 3), placebo subjects fell asleep earlier on N1 (SOL: - 8 min, p < 0.05), but they fell asleep later on N4, N5 and N6 (SOL: + 18, + 30 and + 28 min, respectively; p < 0.05). SOL of SRC subjects was not shortened on N1, but it was lengthened
at the end of the treatment (N4: + 29 min, p < 0.05; N5: + 11 min, p < 0.05); by contrast, SOL of MLT subjects did not change throughout the recovery period.

- For non-REM sleep, compared to baseline, SWS (Fig. 4) was longer in subjects receiving placebo and to a lesser degree in those receiving MLT on N1 (PBO: + 53 min, MLT: + 33 min, p < 0.05), N2 (PBO: + 69 min, MLT: + 28 min, p < 0.05) and N5 for PBO subjects only (+ 37 min, p < 0.05). SWS also appeared significantly earlier (SWS latency decreased) in all these subjects on these nights. This rebound in SWS was observed at the expense of stage 2, which decreased in PBO subjects on N2, N3 and N5 by 86, 65 and 44 min (p < 0.05) and also decreased under MLT on N1, N2 and N4 (- 18, -20, -31 min, p < 0.05). In contrast, in the subjects receiving SRC, SWS did not occur earlier (it was even delayed in N4 by 17 min, p < 0.05) and the rebound in SWS was postponed to N6, the night following the end of drug administration (SWS: + ~21 min, p < 0.05).

- REM sleep (Fig. 5) decreased by 29 min in PBO subjects on N1 (p < 0.05) and by 24, 15 and 25 min under MLT on N1, N2, N3 (p < 0.05). The expected rebound in REM sleep was observed on N2 in PBO subjects only (+ 22 min, p < 0.05); it also came earlier than in baseline conditions (REM sleep latency: - 49 min; p < 0.05). By contrast, no modification of REM sleep was observed under SRC throughout the recovery period.

We observed only a few significant differences between drug conditions within each night. On N1, compared with PBO, stage 1 was increased under SRC (+ 8 min, p < 0.05) and decreased under MLT (~ 8 min, p < 0.05). Stage 2 under MLT was longer than in the other subjects on N3 (p < 0.05). The rebound of SWS on N2 was shorter in MLT than in PBO subjects (p < 0.05).


**Subjective aspects of sleep**

Sleep logs also identified few differences between the drug groups on any given night. We observed on N1, that SRC subjects woke up earlier, slept less long and complained of more awakenings than did the MLT group (p < 0.05), whereas MLT subjects fell asleep earlier and slept longer than did the PBO group (p < 0.05). Wake up of the SRC group was more difficult than for the PBO group on N5 (p < 0.05), and sleep under SRC was longer and better than in the MLT group on N6 (p < 0.05).

Comparisons between recovery nights with baseline data within each drug group did not show the differences observed with the EEG recordings. In PBO subjects, TST was decreased on N4 (p = 0.031). Under SRC, TST was also decreased on N4 (p = 0.039), but increased on N6 (p = 0.027) at the end of the treatment, whereas the quantity of sleep and the quality of dreams and wake up seemed to be insufficient or impaired on N2 (p = 0.011), N3 (p = 0.029) and N5 (p = 0.034). Under MLT, TST appeared shorter on N1 (p = 0.022), quality of sleep better on N1 and N2 (p = 0.013 and 0.034, respectively), quality of dreams worse on N3 (p = 0.022) with a lower duration of sleep on N2 (p = 0.034) and higher quality of wake up on N2 (p = 0.034).

**Daytime sleepiness**

Neither objective nor subjective measurements of sleepiness showed any significant gender effect.

**Objective measures of sleepiness**

Sleep latencies tests (SLT) over baseline and recovery periods are shown in Fig. 6. Compared to baseline, PBO subjects were significantly drowsier until D6 (p < 0.05 to 0.0001, according to the recovery day) and also at D9 a.m. (p < 0.01) and D10 p.m. (p < 0.05).
Conversely, SRC subjects were not sleepy during the period that the drug was given (D1-D5), except on D1 and D2 p.m., where sleep latencies were reduced (p < 0.05). However, sleep latencies were higher under SRC than under PBO on D1 p.m. (424 s ± 114 vs 74 s ± 17, p < 0.05) and D2 a.m. (736 s ± 155 vs 272 s ± 50, p < 0.05). This stimulating effect, compared with PBO, tended to be maintained until D6 (NS). Thereafter, compared with baseline, SRC subjects were sleepier from D6, i.e. at the end of the treatment (p < 0.05 to 0.001 depending on the day).

Under MLT, the subjects were sleepier (sleep latencies significantly decreased, p < 0.001 to 0.05) than in the baseline condition over the entire recovery period during which the drug was taken (D1-D3). Subsequently, sleep latencies did not differ from baseline on D4-D5, decreased again till D8 a.m. (p < 0.01 to 0.05) and returned to baseline level until D10 a.m.

Wrist actigraphic measures reflected normal daytime and nighttime profiles in accordance with the time-table of the experiment (rest/test periods) in all subjects throughout the study (Fig. 7). There was no significant difference in wrist activity between drug conditions within each recovery day. Comparisons between recovery and baseline did not show any difference for PBO and MLT subjects, but with SRC, overall daytime activity was higher (p < 0.05) from D1 to D5, i.e. over the entire recovery period that SRC was taken. Otherwise, nighttime activity was not altered with SRC, which as indicated by the EEG measurements also showed that sleep was not fragmented under SRC.

**Subjective measures of sleepiness**

There was no significant difference between the three drug groups regarding the awake/sleepy item on Bond and Lader's visual analog scale (VAS), except on D1 a.m., where SRC subjects were sleepier than the MLT group (Fig. 8).

VAS confirmed the sleepiness shown by SLT in PBO subjects on D1 a.m. and p.m. only (p < 0.05 and p < 0.01, respectively), but not for the remaining recovery period during which subjects felt more awake on D2 a.m., D5 p.m., D6 a.m. and D8 a.m., compared with baseline
SRC subjects felt sleepier in D1 a.m. only (p < 0.0001), but were less sleepy in the afternoon of D3 (p < 0.05), D4 and D8 (p < 0.01), D9 and D10 (p < 0.001). Under MLT, subjects felt sleepier only on D1 p.m. (p < 0.001), but not on D2 and D3 as shown by SLT. No significant differences were observed between the three drug groups within each day of the study, except for the MLT subjects who felt less sleepy during the flight (p < 0.05) than the two other groups of subjects who had not taken any active drug (they included the SRC subjects whose treatment began on the morning of D1). MLT subjects were also less sleepy than SRC subjects on D1 a.m. (p < 0.05).

Oral temperature

All subjects were synchronized in the USA (the trough of temperature was at 7:00 and the peak occurred between 17:00 and 19:00), and were obviously desynchronized after the flight (trough at 11:00 and peak at 21:00, local time). Basically, resynchronization of temperature is defined as an advance of the trough (batyphase) and the peak (acrophase) of the rhythm. While the peak of temperature occurred at changeable times all over the recovery, we observed that the reentrainment of the trough began from D5 in placebo subjects but still remained partial the last day of the study (trough at 9:00), whereas it was complete from D2 in MLT subjects (trough at 7:00) and began from D3 to the end of the treatment in SRC subjects. Thus, the resynchronization of oral temperature seemed to be faster under melatonin and to a less degree under SRC than with placebo, at least for the batyphase of the rhythm of temperature.
DISCUSSION

A field study to evaluate the effects of jet-lag and sleep deprivation may be difficult to compare with carefully controlled laboratory studies. Our results argue that SRC alleviates daytime sleepiness but exerts some unwanted effects on sleep. By contrast, MLT improves sleep but does not objectively mitigate sleepiness.

We did not observe any sleep disturbances during the baseline night, indicating absence of a first night effect (1). This was expected as our subjects spent five days and nights in Texas for synchronization before the day and night baseline period began. The sleep measures were in agreement with literature data for the range of ages of the subjects (12).

Our subjects experienced the deleterious effects of jet-lag combined with sleep deprivation. The sleep architecture of PBO subjects was disturbed during the first recovery night with a greater duration of SWS at the expense of REM sleep (14). Indeed, REM sleep tends to be predominant at the end of the night, but due to a phase advance of sleep rhythms, our PBO subjects woke up before getting the full amount of REM sleep. Hence, PBO subjects were sleepy during the first recovery daytime, in accordance with data from previous studies (35).

The SWS and REM sleep debt mounted during the flight and the 1st recovery day but was totally re-established after the three following nights so that overall sleep architecture was normalized from the fifth recovery day with an absence of sleepiness after D6, as shown by SLT. This is consistent with the mean reentrainment shift rate for the sleep/wake cycle which is about 1 h/day after an eastbound flight (5), or seven days for a 7-h eastbound flight as in our study. The PBO subjects also demonstrated that the resynchronization of rhythms on D5 was complete for melatonin and partial for cortisol (25) and central temperature, in accordance with previous data (13, 15).
We used 5-mg melatonin (MLT) per dose in accordance with the protocol for alleviating jet-lag proposed by Arendt et al. (4): when going east, intake of one 5-mg capsule of melatonin on departure day and if necessary on the flight, at 18:00 local time and on arrival at local bedtime (22:00-23:00) for 4 days. In any case, a dose above 5 mg (10 mg daily) would not have been fully cleared from the circulation after a 8-h sleep (11) and a lower dose would have been less effective in alleviating jet-lag-related sleep disorders (32).

In our study, melatonin (MLT) improved subjective measures of sleep and sleepiness, in accordance with literature data (3). Self-reports showed that our MLT subjects fell asleep earlier and slept longer than did our PBO subjects. Looking at objective sleep measurements, it has been reported that MLT shortened sleep onset latency (SOL) and SWS duration (37), without modifying REM sleep duration but sometimes lengthening it (8). By contrast, in our MLT subjects, SOL was not shortened and SWS was increased at the expense of REM sleep. This discrepancy could be explained in part by the high individual variability in the pharmacokinetics of melatonin, which may give rise to marked differences in sensitivity (2). Moreover, the hypnotic effects of MLT on the sleep EEG are short-lived, even though melatonin levels are high at the time of sleep onset (9). Sleep onset is known to take place during the descending phase of temperature after acrophase occurred. In our MLT subjects as in the other groups, the acrophase of the temperature rhythm was not clearly reentrained, which may also explain that SOL was not shortened. Lastly, our subjects were somewhat sleep deprived for about 33 hours (time between the end of the last baseline night and the beginning of the 1st recovery night) as we prohibited them from sleeping during the flight. As for our placebo subjects, there was a significant sleep debt, which may account for the fact that, despite the intake of MLT, SWS sleep increased during the first two recovery nights, resulting in a decrease in REM sleep. In fact, under jet-lag conditions there is little evidence
for a phase shifting action of melatonin on objective markers of human circadian rhythms (28) such as sleep. SLT showed that our MLT subjects were sleepy until the last intake of MLT (D3), while visual analog scales showed they were sleepy up to D1.

In contrast with literature data (32), MLT failed to decrease sleepiness in our subjects. It should be borne in mind that MLT improves vigilance and alertness after jet-lag in non-sleep-deprived subjects. In our subjects, the sleepiness may have stemmed more from the sleep deprivation than a residual hypnotic effect of MLT as saliva and thus plasma levels of melatonin of our MLT subjects were comparable to those of the SRC and PBO subjects (30 pg/ml in saliva, measured at 07:00) (25).

The alerting effect of SRC was particularly evident as the subjects could sleep for the 7 hour 30 minute allotted sleep time and so were not sleep deprived (20). Nevertheless, this alerting effect was not observed on the morning of the 1st recovery day where sleep latencies and the feeling of sleepiness were higher than in baseline conditions, although motor activity was maintained. This could be accounted for by the kinetics of SRC (Fig. 1): the minimal efficacy level of caffeine was probably not reached at SLT time (9:00), one hour after SRC intake. As soon as the treatment was stopped, subjects were as sleepy as in the baseline condition, consistent with the fact that the subjective (VAS) and objective (SLT) efficacy of 300-mg SRC is lost 9-13 hours following intake.

The alerting effect of SRC seemed to induce some residual effects on recovery sleep, indicated by less SWS rebound in N1-N2 and increased nighttime wakefulness in N1 (+ ~25 min, not significant) compared with PBO and MLT subjects. Moreover, sleep logs showed that SRC subjects woke up earlier, slept less and complained of more awakenings than did the MLT group during N1. In addition, the rebound in SWS was postponed to N6 at the
beginning of SRC withdrawal, whereas WASO fell on N5, the night following last intake (D5, see fig. 2) and continued to be low until the end of the study. These observations suggest that subjects were sleep-deprived under SRC. Caffeine levels in saliva samples were measured three times per day (7:00, 12:00, 22:00) throughout the study (25). At 22:00, i.e. 14 hours after intake, salivary SRC was 2 µg/ml corresponding to a plasma level of 2.7 µg/ml, based on a saliva/plasma ratio of 0.74 (30). This level was higher than the plasma level of caffeine effectiveness (2.5 µg/ml, see fig. 1), and may possibly explain the disturbances of sleep in the recovery period.

CONCLUSION

Slow-release caffeine and melatonin may be of value for alleviating some symptoms related to conditions including an eastbound jet lag combined with sleep deprivation. MLT decreases sleepiness subjectively but not objectively, and improves recovery sleep. The most notable effect of SRC is to reduce sleepiness for a few days with however some unwanted effects on recovery sleep. Further studies on jet-lag without concomitant sleep deprivation will be required to evaluate fully the effects of slow release caffeine compared to melatonin on recovery sleep and sleepiness following an eastbound flight.
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REFERENCES


Figure legends

Fig. 1. Pharmacokinetics of 300-mg slow release caffeine (SRC) compared with two cups of espresso coffee (128 mg caffeine); from M. Enslen, Nestec SA, Nestlé Research Center, unpublished data.

Fig. 2. Experimental protocol. On D1 (17:00, US time), D0 (16:00, US time) and D1-D3 (23:00, French time) MLT subjects were given 5-mg melatonin and the other groups were given placebo. On D1-D5 (08:00, French time), SRC subjects were given 300-mg slow release caffeine and the other groups were given placebo.

Fig.3. Sleep onset latencies (SOL) in PBO, MLT and SRC groups over baseline (N-1) and recovery nights (N1-N10). *, **: significant difference between each recovery night and the baseline night within each drug group (p < 0.05; p < 0.01, respectively). Values are expressed in minutes (mean ± SEM).

Fig.4. SWS duration in PBO, MLT and SRC groups over baseline (N-1) and recovery nights (N1-N10). *: significant difference between each recovery night and the baseline night within each drug group (p < 0.05); +: significant difference between drug conditions (p < 0.05) within each recovery night. Values are expressed in minutes (mean ± SEM).

Fig.5. REM sleep duration in PBO, MLT and SRC groups over baseline (N-1) and recovery nights (N1-N10). *: significant difference between each recovery night and the baseline night within each drug group (p < 0.05). Values are expressed in minutes (mean ± SEM).

Fig. 6. Daytime sleepiness assessed by measurements of sleep latencies (SLT) in PBO, MLT and SRC groups over baseline and recovery days. *, **, ****: significant difference between each recovery day and the baseline day (D1) within each drug group (p < 0.05; p < 0.01; p <
0.0001, respectively); +: significant difference between drug conditions (p < 0.05) within each recovery day (D1-10); Sleep latencies are expressed in s (mean ± SEM).

Fig. 7 Wrist actigraphy (movements per hour) of PBO (triangle), MLT (square) and SRC (diamond) subjects throughout baseline and recovery nights and days. Measures reflect a normal activity profile; a: wake up then breakfast; b: morning tests; c: lunch; d: afternoon tests; e: dinner then moving to the bedroom; f: night time. *: significant difference between recovery and baseline days and nights within each drug group (p < 0.05).

Fig. 8 Subjective assessment of vigilance on Bond and Lader's visual analog scale (item awake/sleepy). *, **, ***, ****: significant difference between recovery days and the baseline day (D-1) within each drug group (p < 0.05; p < 0.01; p < 0.001; p < 0.0001, respectively); +: significant difference between drug conditions (p < 0.05) within each recovery day (D1-10). Scale is graduated in mm (mean ± SEM).
Table 1.- Sleep measures (mean ± SD) in SRC, MLT and PBO groups from baseline night (N-1) to the last recovery night (N9). Comparison between recovery nights and baseline night using the * (p < 0.05) or the ** (p < 0.01) symbol. Comparisons between drugs in a given night using the § (p < 0.05).
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Table 1 (end).
Figure 1

- **SRC (300 mg)**
- **Coffee (2 x 64 mg of caffeine)**

**µg caffeine / ml plasma**

**Threshold for unwanted effects**

**Threshold for alerting effects**

Ingestion
Figure 2
Figure 3

Last intake of MLT: 23:00
Last intake of SRC 07:00

Sleep onset latency (min)

- MLT
- PBO
- SRC

Nights

N-1 N1 N2 N3 N4 N5 N6 N7 N8 N9
Figure 4

Last intake of MLT: 23:00
Last intake of SRC: 07:00
Figure 5

Last intake of MLT: 23:00
Last intake of SRC: 07:00

REM sleep duration (min)
Figure 6

Sleep latencies (s)

Last intake of MLT: 23:00

Last intake of SRC: 07:00

FLIGHT

Clock time

SRC
MLT
PBO

0 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300

9 14 9 14 9 14 9 14 9 14 9 14 9 14 9 14 9 14
D-1 D0 D1 D2 D3 D4 D5 D6 D7 D8 D9 D10
Figure 7

Last intake of MLT: 23:00

Last intake of SRC: 07:00

Mvts/hour

Time (clock hours)
Figure 8

Measure (min)

Last intake of MLT: 23:00

Last intake of SRC: 07:00

FLIGHT

SRC

MLT

PBO

Awake

Sleepy

Clock time

D-1 D0 D1 D2 D3 D4 D5 D6 D7 D8 D9 D10