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

M. Beaumont, D. Batéjat, C. Piérad, P. Van Beers, J. B. Denis, O. Coste, P. Doireau, F. Chauffard, J. French, and D. Lagarde. Caffeine or melatonin effects on sleep and sleepiness after rapid eastward transmeridian travel. *J Appl Physiol* 96: 50–58, 2004. First published September 5, 2003; 10.1152/japplphysiol.00940.2002.—We measured the effects of slow-release caffeine (SRC) and melatonin (Mlt) on sleep and daytime sleepiness after a seven-time zone eastbound flight. In a double-blind, randomized, placebo-controlled study, each of three groups of nine subjects was given either 300 mg SRC on recovery day 1 (D1) to D5 (0800) or 5 mg Mlt on preflight D−1 (1700), flight day D0 (1600), and from D1 to D3 (2300), 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 with baseline, we found a significant rebound of slow-wave sleep on night 1 (N1) to N2 under Pbo and Mlt and a significant decrease in rapid eye movement 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 after an eastbound flight: SRC on daytime sleepiness, and Mlt on sleep.

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 (Mlt), 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 2000 and 2100 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 ~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 that there is a possible role of caffeine on circadian rhythmicity by acting on A2b adenosine receptors of the pineal gland (36). We hypothesized that Mlt and SRC could, respectively, improve sleep and mitigate daytime sleepiness after 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 seven-time zone eastbound flight, by using subjective and objective methods. This work was part of a large, real-world French-American study called “Operation Pegasus” in which ~140 physiological, psychological, and biological parameters were measured (18, 25).

METHODS

Subjects

This double-blind, randomized, placebo (Pbo)-controlled study was conducted on 27 healthy volunteers from a US Air Force Reserve Unit that was representative of the US population (18 men and 9 women; 15 Caucasians, 9 Hispanics, and 3 African-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 (16) showed that they were neither morning nor evening types; they habitually went to bed between 2300 and 2400 h and woke up between 0600 and 0700 h with a sleep duration ranging from 6.5 to 7.5 h. They had not experienced a transmeridian flight in the 2 mo before their enrollment in this study. They were nonsmokers and did not consume large amounts of xanthine-based beverages on a regular basis (coffee, tea, and cola: equivalent to <3 cups/day), nor had they taken psychotropic drugs or Mlt in the 3 mo before 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 before 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

See Fig. 2. The subjects were housed and trained at Brooks Air Force Base in San Antonio, Texas over 6 days, and their routines were identical. During the first 5 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...
Subjects were given 300 mg SRC, and the other groups were given Pbo.

SLT, sleep latencies test; MSLT, multiple sleep latencies test.

Fig. 2. Experimental protocol. On baseline (D–1) and day (D) 1 to avoid the first-night effect (1). The flight was scheduled on day 0 (D0) at 1500 (US time) for a seven-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 h from last awakening at Brooks Air Force Base 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 at 0600 (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 0700 (beginning of light exposure), breakfast at 0800, morning tests between 0900 and 1200, lunch between 1230 and 1330, evening tests between 1400 and 1700, light muscular activity (walking in the woods) between 1730 and 1830, dinner at 1930, 0800, morning tests between 0900 and 1200, lunch between 1230 and 1330, evening tests between 1400 and 1700, light muscular activity (walking in the woods) between 1730 and 1830, dinner at 1930, fitting of EEG electrodes from 2000, leisure (reading, games) until bedtime, which was impossible, some women refused to wear the cap every night. Moreover, we knew, from having used this device in a previous study (17), that, in our long-haired female subjects, electric signals would have likely been 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, to maintain our group of subjects as homogeneous as possible, we decided to discard all of 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 latency (<15 min, 15–30 min, 30–45 min, >45 min), awakenings and sleep periods (noted on a 24-h scale with a precision of 15 min), sleep quality (light, intermediate, deep), dream quality (pleasant, unpleasant...)

Fig. 1. Pharmacokinetics of 300 mg slow-release caffeine (SRC) compared with 2 cups of espresso coffee (128 mg caffeine). (Figure provided by M. Enslen, Nestec SA, Nestlé Research Center.)

Measurements

Sleep. Baseline and recovery sleep architecture was assessed from standard polysomnographic recordings, including electroencephalography (C3/C4, O3/O2, referenced to an A1 ground electrode on the mastoid apophysis), electrooculography of each eye (oblique and horizontal derivations), and chin electromyography. Polysomnography electric signals were recorded by using TEAC recorders (Tekelc France, Sèvres, France) and were then sampled, amplified, and stored by using a portable Medilog 9000–2 (Oxford Medical Instruments, Abingdon, UK) from 2300 to 0700 during the baseline (N–1) 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 Pbo). We calculated the following 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 (TST-to-time in bed ratio), and sleep onset latency (SOL) (time from lights out to first episode of stage 2). We also measured slow-wave sleep (SWS) and rapid eye movement (REM) sleep latencies (time from first stage 2 to first epochs of stage 3 and REM sleep, respectively). Each stage of sleep was analyzed by measuring total duration and percentage of TST; the number of SWS and REM sleep episodes were also counted.

For this long (~2 wk) field study, sticking electrodes on the skull by 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, which was impossible), some women refused to wear the cap every night. Moreover, we knew, from having used this device in a previous study (17), that, in our long-haired female subjects, electric signals would have likely been lost or of a poor quality. We were unable to check directly the quality of the signals. For these reasons, the too small-sized female population would have been recorded in good conditions, and, to maintain our group of subjects as homogeneous as possible, we decided to discard all of 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 on a 24-h scale with a precision of 15 min), sleep quality (light, intermediate, deep), dream quality (pleasant, unpleasant...)

Fig. 2. Experimental protocol. On baseline day 1 (D–1) (1700, US time), D0 (1600, US time), and D1–D3 (2300, French time), melatonin (Mlt) subjects were given 5 mg Mlt and the other groups were given placebo (Pbo). On D1–D5 (0800, French time), SRC subjects were given 300 mg SRC, and the other groups were given Pbo. SLT, sleep latencies test; MSLT, multiple sleep latencies test. N–6, D–6, N–5: night 6, day 6, and night 5 of familiarization period; N–1 and D–1, last night and day when baseline data were obtained.

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ant), 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 a nonstandardized multiple SLT (10), because sleep latencies were measured with only two naps (at 0900 and 1400). As for a multiple SLT, 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 three consecutive 30-s epochs of stage 1 sleep, one first 30-s epoch of stage 2 sleep, or 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 nondominant wrist throughout the experiment. The number of movements with a force >0.1 G was counted and then was averaged over the following periods: 0700–0900, 0900–1200, 1200–1400, 1400–1700 (afternoon test period), 1700–1900, 1900–2300, 2300–0300, and 0300–0700.

Sleepiness was subjectively evaluated by the “sleepy-awake” item from Bond and Lader’s (7) visual analog scales (VAS) during baseline and recovery periods and also during the flight, 1, 3, and 5 h after drug intake (1600).

Except for continuous actigraphy, these objective and subjective measurements were taken at 0900 and 1400, corresponding to the hyper- and hypovigilance periods defined by Lavie (19).

**Oral temperature.** 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 0700 (wake up) and 2300 (bedtime), by using an electronic thermometer.

### Statistical Analysis

Sleep and sleepiness data were analyzed separately and compared by two-way ANOVA (drug: SRC, Mlt, Pbo; 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, by using a Newman-Keuls test.

### RESULTS

#### Sleep Architecture

**Baseline sleep.** Because 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 Pbo, see METHODS). There were no significant differences in sleep parameters among the subjects of these three groups (Table 1).

**Recovery sleep.** See Table 1. When data measured during recovery from standard deviation within each drug group are compared, 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 for SPT, which fell by ~30 min in the SRC group on N4 (P < 0.05). However, compared with baseline, SRC subjects increased their WASO by ~40 and 20 min on N3 and N4, respectively, and then dropped ~40 min in N5, although these changes did not reach significance. Because TST and time in bed were constant for all subjects, sleep efficiency index did not vary throughout recovery in any of the groups.

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

For sleep latency (SOL, Fig. 3), Pbo 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 with baseline, SWS (Fig. 4) was longer in subjects receiving Pbo 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 of 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, respectively (P < 0.05), and also decreased under Mlt on N1, N2, and N4 (−18, −20, and −31 min, respectively; 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 after the end of drug administration (SWS: plus ~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, and N3, respectively (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
Table 1. Sleep measures in SRC, Mlt, and Pbo groups from baseline night (N = 1) to the last recovery night (N9)

| Nights | Drug | Drug | WASO, min | SPT, min | SEL % | SOL, min | Stage 1, min | Stage 2, min | Stage 3, min | Stage 4, min | SWS, min | NREM Sleep, min | REM Sleep, min | No. of SWS Episodes | Duration of SWS Episodes, min | SWS Latency, min | No. of REM Sleep Episodes | Duration of REM Sleep Episodes, min | REM Sleep Latency, min | Values are means ± SD, N = 1, baseline night; N1–N9, nights 1–9; SRC, slow-release caffeine; Mlt, melatonin; Pbo, placebo; SPT, sleep period time; WASO, wakefulness after sleep onset; TST, total sleep time; SEL, sleep efficiency index; SOL, sleep onset latency; SWS, slow-wave sleep; REM, rapid eye movement; NREM, non-REM. Significant difference between recovery and baseline nights: *P < 0.05, **P < 0.01. Significant difference between drugs in a given night, 1P < 0.05. |
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.* SLT over baseline and recovery periods are shown in Fig. 6.

Compared with baseline, Pbo subjects were significantly drowsier until D6 ($P < 0.05$ to 0.0001, according to the recovery day) and also at D9 AM ($P < 0.01$) and D10 PM ($P < 0.05$).

Conversely, SRC subjects were not sleepy during the period that the drug was given (D1–D5), except on D1 and D2 PM, when sleep latencies were reduced ($P < 0.05$). However, sleep latencies were higher under SRC than under Pbo on D1 PM ($424 \pm 114$ vs. $74 \pm 17$ s; $P < 0.05$) and D2 AM ($736 \pm 155$ vs. $272 \pm 50$ s; $P < 0.05$). This stimulating effect, compared with Pbo, tended to be maintained until D6 (not significant). 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 until D8 AM ($P < 0.01$ to 0.05), and returned to baseline level until D10 AM.

Wrist actigraphic measures reflected normal daytime and nighttime profiles, in accordance with the time table of the experiment (rest and 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 among the three drug groups regarding the awake/sleepy item on Bond and Lader’s VAS (7), except on D1 AM, when SRC subjects were sleepier than the Mlt group (Fig. 8).

VAS confirmed the sleepiness shown by SLT in Pbo subjects on D1 AM and PM only ($P < 0.05$ and $P < 0.01$, respectively), but not for the remaining recovery period, during which subjects felt more awake on D2 AM, D5 PM, D6 AM, and D8 AM, compared with baseline ($P < 0.05$). SRC subjects felt sleepier in D1 AM only ($P < 0.0001$), but were less sleepy in the afternoon of D3 ($P < 0.05$), D4 and D8 ($P < 0.01$), and D9 and D10 ($P < 0.001$). Under Mlt, subjects felt sleepier only on D1 PM ($P < 0.001$), but not on D2 and D3 as shown by SLT.

No significant differences were observed among 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 AM ($P < 0.05$).

**Oral Temperature**

All subjects were synchronized in the USA (the trough of temperature was at 0700, and the peak occurred between 1700 and 1900) and were obviously desynchronized after the flight (trough at 1100 and peak at 2100, 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 Pbo subjects but still remained partial the last day of the study (trough at 0900), whereas it was complete from D2 in Mlt subjects (trough at 0700) and began from D3 to the end of the treatment in SRC subjects. Thus the resynchronization of oral temperature seemed to be faster under Mlt and to a less degree under SRC than with Pbo, 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 5 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

![Fig. 6. Daytime sleepiness assessed by measurements of sleep latencies in Pbo, Mlt, and SRC groups over baseline and recovery days. Values are means ± SE in seconds. Significant difference between each recovery day and the baseline day (D−1) within each drug group: *$P < 0.05$; **$P < 0.01$; ****$P < 0.0001$. *Significant difference between drug conditions ($P < 0.05$) within each recovery day (D1–D10).](image)

![Fig. 7. Wrist actigraphy [movements (Mvts) per hour] of Pbo ( ), Mlt ( ), and SRC ( ) subjects throughout baseline and recovery nights and days. Measures reflect a normal activity profile. a Wake up and then breakfast; b morning tests; c lunch; d afternoon tests; e dinner and then moving to the bedroom; f nighttime. *Significant difference between recovery and baseline days and nights within each drug group, $P < 0.05$.](image)
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 first recovery day but was totally reestablished after the 3 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 ~1 h/day after an eastbound flight (5), or 7 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 Mlt and partial for cortisol (25) and central temperature, in accordance with previous data (13, 15).

We used 5 mg 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 Mlt on the departure day and, if necessary, on the flight, at 1800 local time, and on arrival at local bedtime (2200–2300) for 4 days. In any case, a dose >5 mg (10 mg daily) would not have been fully cleared from the circulation after an 8-h sleep (11) and a lower dose would have been less effective in alleviating jet lag-related sleep disorders (32).

In our study, 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 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 Mlt, 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 Mlt 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 why SOL was not shortened. Last, our subjects were somewhat sleep deprived for ~33 h (time between the end of the last baseline night and the beginning of the first recovery night), as we prohibited them from sleeping during the flight. As for our Pbo subjects, there was a significant sleep debt, which may account for the fact that, despite the intake of Mlt, SWS increased during the first 2 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 Mlt 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), whereas VAS showed that they were sleepy up to D1.

In contrast to 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 Mlt of our Mlt subjects were comparable to those of the SRC and Pbo subjects (30 pg/ml in saliva, measured at 0700) (25).

The alerting effect of SRC was particularly evident as the subjects could sleep for the 7 h 30 min allotted sleep time and so were not sleep deprived (20). Nevertheless, this alerting effect was not observed on the morning of the first recovery day, when 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 (0900), 1 h 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 h after 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 (plus ~25
The most notable effect of SRC is to reduce sleepiness for a combined with sleep deprivation. Mlt decreases sleepiness 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 (0700, 1200, 2200) throughout the study (25). At 2200, i.e., 14 h after intake, salivary SRC was 2 μg/ml, corresponding to a plasma level of 2.7 μg/ml, based on a saliva-to-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

SRC and Mlt may be of value for alleviating some symptoms related to conditions, including an eastbound jet lag recovery period. Further studies on jet lag without concommitant sleep deprivation will be required to evaluate fully the effects of SRC compared with M1t on recovery sleep and sleepiness after an eastbound flight.

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