Aviat Space Environ Med. 2001 Nov;72(11):974-84.

Melatonin and zopiclone as pharmacologic aids to facilitate crew rest.

Paul MA, Brown G, Buguet A, Gray G, Pigeau RA, Weinberg H, Radomski M.

Source

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Abstract

PURPOSE: In response to mission imperatives, transport aircrews must often sleep at inappropriate circadian times resulting in inadequate sleep. This study was undertaken to determine whether either melatonin or zopiclone could facilitate early circadian sleep, and to assess whether either of these medications would result in a psychomotor performance decrement which would preclude their use in aircrew.

METHOD: Thirteen subjects from DCIEM completed a double-blind cross-over protocol. All subjects were assessed for psychomotor performance during 3 drug conditions (placebo, 10 mg melatonin, and 7.5 mg zopiclone), which were separated by one week. Each of these conditions involved 2 nights of sleep, back-to-back, with the first night being a normal circadian control sleep (23:00 h bedtime, arising at 06:45 h), and the second night being an early circadian drug sleep (drugs at 16:45 h, 17:00 h bedtime, arising at 23:45 h). All subjects were tested for psychomotor performance, on both nights of each of the 3 drug conditions, pre- and post-sleep. Further, during the early circadian drug night, all subjects were tested every hour after arising at 23:45 h (24:00 h until 07:00 h. At the beginning of each psychomotor test session, subjects were asked for their subjective levels of sleepiness and fatigue.

RESULTS: Relative to placebo (339.5 min) the subjects slept more on melatonin (370.2 min, $p < 0.01$), and zopiclone (373.3 min, $p < 0.01$). Performance in serial reaction time (SRT) task ($p < 0.001$), logical reasoning task (LRT) ($p < 0.001$), serial subtraction task (SST) ($p < 0.02$), and Multitask (MT) ($p < 0.03$) were impaired for all 3 drug conditions immediately on awakening, compared with pre-sleep performance, as a result of a sleep-inertia effect. With respect to the subjective data, sleep inertia effects were evident for sleepiness ($p < 0.001$), mental fatigue ($p < 0.002$), and physical fatigue ($p < 0.05$). For SRT, LRT, and SST, performance recovered to pre-sleep levels within 1.25 h of awakening, and for MT recovery occurred 2.25 h after awakening. There were no differences in performance or subjective measures between placebo, melatonin and zopiclone.

CONCLUSIONS: Both zopiclone and melatonin improved sleep relative to placebo. After sleep inertia, performance recovered to pre-sleep levels for all tasks and was sustained at that level throughout the balance of the testing period. There was no impact of melatonin or zopiclone on performance measures compared with placebo.

PMID: 11718517 [PubMed - indexed for MEDLINE]

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Cochrane Database Syst Rev. 2002;(2):CD001520.

Melatonin for the prevention and treatment of jet lag.

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Source

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Abstract

BACKGROUND: Jet-lag commonly affects air travellers who cross several time zones. It results from the body's internal rhythms being out of step with the day-night cycle at the destination. Melatonin is a pineal hormone that plays a central part in regulating bodily rhythms and has been used as a drug to re-align them with the outside world.

OBJECTIVES: To assess the effectiveness of oral melatonin taken in different dosage regimens for alleviating jet-lag after air travel across several time zones.

SEARCH STRATEGY: We searched the Cochrane Controlled Trials Register, MEDLINE, EMBASE, PsychLit and Science Citation Index electronically, and the journals 'Aviation, Space and Environmental Medicine' and 'Sleep' by hand. We searched citation lists of relevant studies for other relevant trials. We asked principal authors of relevant studies to tell us about unpublished trials. Reports of adverse events linked to melatonin use outside randomised trials were searched for systematically in 'Side Effects of Drugs' (SED) and SED Annuals, 'Reactions Weekly', MEDLINE, and the adverse drug reactions databases of the WHO Uppsala Monitoring Centre (UMC) and the US Food & Drug Administration.

SELECTION CRITERIA: Randomised trials in airline passengers, airline staff or military personnel given oral melatonin, compared with placebo or other medication. Outcome measures should consist of subjective rating of jet-lag or related components, such as subjective wellbeing, daytime tiredness, onset and quality of sleep, psychological functioning, duration of return to normal, or indicators of circadian rhythms.

DATA COLLECTION AND ANALYSIS: Ten trials met the inclusion criteria. All compared melatonin with placebo; one in addition compared it with a hypnotic, zolpidem. Nine of the trials were of adequate quality to contribute to the assessment, one had a design fault and could not be used in the assessment. Reports of adverse events outside trials were found through MEDLINE, 'Reactions Weekly', and in the WHO UMC database.

MAIN RESULTS: Nine of the ten trials found that melatonin, taken close to the target bedtime at the destination (10pm to midnight), decreased jet-lag from flights crossing five or more time zones. Daily doses of melatonin between 0.5 and 5mg are similarly effective, except that people fall asleep faster and sleep better after 5mg than 0.5mg. Doses above 5mg appear to be no more effective. The relative ineffectiveness of 2mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. Based on the review, the number needed to treat (NNT) is

2. The benefit is likely to be greater the more time zones are crossed, and less for westward flights. The timing of the melatonin dose is important: if it is taken at the wrong time, early in the day, it is liable to cause sleepiness and delay adaptation to local time. The incidence of other side effects is low. Case reports suggest that people with epilepsy, and patients taking warfarin may come to harm from melatonin.

REVIEWER'S CONCLUSIONS: Melatonin is remarkably effective in preventing or reducing jet-lag, and occasional short-term use appears to be safe. It should be recommended to adult travellers flying across five or more time zones, particularly in an easterly direction, and especially if they have experienced jet-lag on previous journeys. Travellers crossing 2-4 time zones can also use it if need be. The pharmacology and toxicology of melatonin needs systematic study, and routine pharmaceutical quality control of melatonin products must be established. The effects of melatonin in people with epilepsy, and a possible interaction with warfarin, need investigation.

Update of
Cochrane Database Syst Rev. 2001;(1):CD001520.
PMID: 12076414 [PubMed - indexed for MEDLINE]

Chronobiol Int. 1998 Nov;15(6):655-66.

Comparative study to determine the optimal melatonin dosage form for the alleviation of jet lag.

Suhner A, Schlagenhauf P, Johnson R, Tschopp A, Steffen R.

Source

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Abstract

To compare the impact of various dosage forms of melatonin and placebo on jet lag symptoms, 320 volunteers who had flights over 6 to 8 time zones were recruited for a double-blind, randomized, placebo-controlled study. The volunteers received either melatonin 0.5-mg fast-release (FR) formulation, melatonin 5-mg FR formulation, melatonin 2-mg controlled-release (CR) formulation, or placebo. The study medication was taken once daily at bedtime during 4 days after an eastward flight. The volunteers completed the Profile of Mood States (POMS), sleep log, and symptoms questionnaires once daily and the Karolinska Sleepiness Scale (KSS) three times daily prior to departure and during the 4 days of medication intake postflight. A total of 234 (73.1%) participants were compliant and completed the study. The FR melatonin formulations were more effective than the slow-release formulation. The 5-mg FR formulation significantly improved the self-rated sleep quality ($p < .05$), shortened sleep latency ($p < .05$), and reduced fatigue and daytime sleepiness ($p < .05$) after intercontinental flight. The lower physiological dose of 0.5 mg was almost as effective as the pharmacological dose of 5.0 mg. Only the hypnotic properties of melatonin, sleep quality and sleep latency, were significantly greater with the 5.0-mg dose.

PMID: 9844753 [PubMed - indexed for MEDLINE]

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Efficacy of Melatonin Treatment in Jet Lag, Shift Work, and Blindness

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Abstract

Melatonin has chronobiotic properties in humans. It is able to phase shift strongly endogenous rhythms, such as core temperature and its own endogenous rhythm, together with the sleep-wake cycle. Its ability to synchronize free-running rhythms has not been fully investigated in humans. There is evidence for synchronization of the sleep-wake cycle, but the available data suggest that it is less effective with regard to endogenous melatonin and core temperature rhythms. When suitably timed, most studies indicate that fast release preparations are able to hasten adaptation to phase shift in both field and simulation studies of jet lag and shift work. Both subjective and objective measures support this statement. However, not all studies have been successful. Careful evaluation of the effects on work-related performance is required. When used to alleviate the non-24-h sleep-wake disorder in blind subjects, again most studies report a successful outcome using behavioral measures, albeit in a small number of individuals. The pres suggest, however, that although leep-wake can be stabilized to 24 h, entrainment of other rhythms is exceptionally rare.

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