Effect of melatonin on jet lag after long haul flights

Keith Petrie, John V Conaglen, Leonard Thompson, Kerry Chamberlain

Abstract

***Objective*—To determine whether doses of the pineal hormone melatonin alleviate jet lag.**

***Design*—Double blind, placebo controlled crossover trial.**

***Setting*—Long haul return flights from Auckland, New Zealand, to London and back.**

***Subjects*—Twenty volunteers with experience of transcontinental flights (eight women and 12 men aged 28 to 68).**

***Interventions*—Melatonin (or placebo) 5 mg three days before flight, during flight, and once a day for three days after arrival.**

***End point*—Symptoms of jet lag.**

***Measurements and main results*—Visual analogue scale for feelings of jet lag and tiredness; profile of moods states questionnaire for vigour-activity and fatigue-inertia; and retrospective ratings 10 days after arrival of sleep pattern, energy, and daytime tiredness. Feelings of jet lag were less for subjects taking melatonin (mean score 2·15 *v* 3·4); these subjects took fewer days than the placebo group to establish a normal sleep pattern (2·85 *v* 4·15), to not feel tired during the day (3·0 *v* 4·6), and to reach normal energy levels (3·25 *v* 4·7). Results for fatigue-inertia and vigour-activity were similar. For all subjects jet lag was more severe on the return (westward) than the outward (eastward) journey.**

***Conclusions*— Melatonin can alleviate jet lag and tiredness after long haul flights.**

Introduction

Jet lag is a common problem for air travellers after a flight through several time zones. It seems to be due to the time required to resynchronise the body's endogenous circadian rhythm to the night and day cycle of the new environment. Disturbed sleep, loss of mental efficiency, and tiredness during the day are commonly reported in the first week or so after a long haul flight.[1] These symptoms seem to increase with the number of time zones crossed,[2] and eastward flights reportedly result in slower adaptation than westward flights.[3]

Recently there has been interest in the role of the pineal hormone melatonin in alleviating jet lag.[4,5] Under normal circumstances melatonin is secreted at night in a 24 hour cycle. Some researchers have proposed that melatonin acts as a synchroniser for several other body rhythms.[6] Thus taking melatonin at times when it should be released naturally might help adaptation to a distant time zone by hastening retraining of the body's endogenous circadian rhythms.

In a double blind trial of melatonin in 17 subjects flying through eight time zones from San Francisco to London significantly fewer subjects taking melatonin reported jet lag.[4] Biochemical data from this study showed that endogenous melatonin and cortisol rhythms resynchronised more rapidly in subjects taking melatonin.[5] The study, however, was limited as jet lag was measured only once (retrospectively on day seven) and subjects travelled only in an easterly direction.

We investigated the effect of melatonin on jet lag after flights from Auckland to London and back. The study was designed so that feelings of jet lag and mood could be closely monitored over the 10 days after the flight, thus allowing closer examination of the readjustment.

Subjects and methods

Twenty volunteers with experience of transcontinental flights through at least five time zones were recruited from our associates, and all completed the study. Each gave informed consent to the study, which was approved by Waikato Hospital's ethics committee. The eight women and 12 men were aged 28 to 68. All subjects flew from Auckland to London in an eastward direction through 12 time zones on a 26 hour flight. They returned on a similar westward flight three weeks later. Subjects travelled in two groups one day apart in both directions.

Subjects were randomly assigned in a double blind procedure to receive melatonin or placebo on the outward flight and the other substance on the return journey. For three days before their flights they took 5 mg of melatonin (in gelatin lactose) or placebo (gelatin lactose) at between 1000 and 1200 local time. They also took a capsule at the same time during the flight and at between 2200 and 2400 (destination time) for three days after their arrival.

On the day before the departure of both flights, on arrival, and at 1600 on days 1-5, 7, and 10 after arrival subjects completed visual analogue ratings of their feelings of jet lag and tiredness. They also completed a profile of moods states questionnaire designed to measure six fluctuating affective states,[7] two of which were relevant to jet lag—namely, vigour-activity and fatigue-inertia. On these occasions they also recorded their hours of sleep over the past 24 hours. On the 10th day after arrival subjects completed a retrospective rating of jet lag on a six point scale ranging from "none at all" to "extreme." At this time subjects also answered questions on how many days it had taken for their sleep pattern and energy to return to normal and until they no longer felt tired during the day. Finally, subjects were asked to guess whether they had taken melatonin or placebo to control for their expectancy influencing rates. Identical procedures were followed on the return trip.

Data were analysed with the statistical package for the social sciences[8] with one way analysis of variance and *t* tests.

Results

Figure 1 shows the visual analogue scores for jet lag reported on days 1-5, 7, and 10 after arrival. The mean

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scores were consistently higher among those taking placebo for the first five days after arrival in both directions. Subjects taking melatonin reported significantly less overall jet lag at the retrospective rating on day 10 than did those taking placebo (mean (SD) score 2·15 (0·99) for melatonin, 3·40 (1·47) for placebo; $F=10·0$, $p<0·01$). Figure 1 also shows that jet lag was more severe on the return journey; this was confirmed by the retrospective ratings, which were significantly higher after the return journey to New Zealand than the trip to London ($t=2·14$, df=19, $p<0·05$).

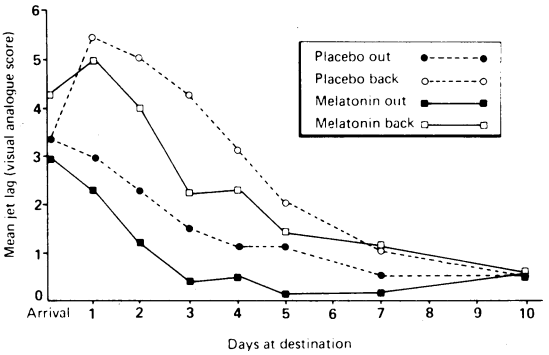

FIG 1—*Reported jet lag in experimental groups after journeys from Auckland to London and back, measured on visual analogue scale (0=none, 10=extreme)*

The table shows the remaining retrospective ratings on day 10—namely, the number of days taken to establish a normal sleep pattern, till subjects did not feel tired during the day, and to reach normal energy levels. Subjects taking melatonin took significantly fewer days than those taking placebo for all these variables ($p<0·05$).

Retrospective ratings on day 10 after flights through 12 time zones in 20 passengers given melatonin or placebo

	Mean (SD) No of days	F	p Value
	Time to normal sleep pattern		
Placebo	4·2 (1·90)	5·39	<0·05
Melatonin	2·9 (1·63)		
	Time to not feeling tired during day		
Placebo	4·6 (2·41)	5·69	<0·05
Melatonin	3·0 (1·78)		
	Time to normal energy level		
Placebo	4·7 (2·27)	5·06	<0·05
Melatonin	3·3 (1·77)		

Scores were obtained on the two relevant scales of the profile of moods states (fatigue-inertia and vigour-activity) by summing individual scale items in accordance with standard scoring procedures.[7] Figure 2 shows the pattern of responses on these two scales from the day of arrival to 10 days later. The scores for both groups showed a similar pattern to the visual analogue and retrospective ratings of jet lag with more vigour-activity and less fatigue-inertia among subjects taking melatonin for the first few days after arrival. In spite of differences in reported fatigue and vigour analysis of the reported hours of sleep each day showed essentially no difference between the groups from the day before departure to seven days after arrival.

When subjects were asked to guess which group they were in (placebo or melatonin) nine subjects on the outward flight did not know, six incorrectly assigned themselves, and five correctly assigned themselves to the melatonin or placebo groups. On the return flight five subjects had no idea, six were incorrect, and nine correctly assigned themselves. This suggested that

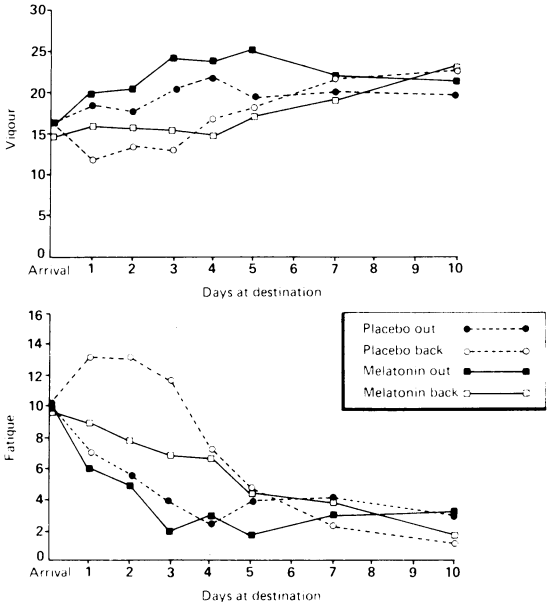

FIG 2—*Mean scores for profile of moods states, vigour-activity (top) and fatigue-inertia (bottom) in experimental groups after journeys from Auckland to London and back*

subjects' ideas of which drug they were taking were unlikely to have biased their response.

Subjects were asked to record any side effects experienced from taking the capsules. Twelve subjects reported no side effects when taking either placebo or melatonin. Two subjects taking melatonin reported a mild sedative effect lasting about a half an hour, and one other reported feeling more relaxed. Among subjects taking placebo one reported increased tiredness, one a greater feeling of relaxation, and one a greater depth of sleep.

Discussion

The results of this study support the use of melatonin as a remedy for jet lag on long haul flights. Subjects taking melatonin reported less jet lag and took less time to recover from their shift across 12 time zones. They also reported that they were less tired during the day and required less time to establish a normal sleeping pattern and reach their normal level of energy.

The effect of melatonin on jet lag may be due to its sedative properties.[9] If this were so subjects taking melatonin would be expected to report longer periods of sleep than those taking placebo, though the effect might also be on the quality of sleep, which would be difficult to quantify. Our finding of no difference in hours of sleep between the groups suggests that melatonin may indeed operate by retraining the endogenous circadian rhythm.

The finding of greater jet lag after the return journey requires further investigation. Previous research on the difference in jet lag after westward and eastward flights has been based on the hypothesis that lengthening the natural circadian rhythm is easier than shortening it, and therefore eastward flights generally cause less disturbance than westward flights.[3] In our study, however, both eastward and westward flight times were across 12 time zones, and the difference in reported jet lag was not explained by the usual phase shifts required after shorter eastward and westward flights. The increased jet lag on the return westward flight may have been an artefact of the homeward journey with its return to a more demanding and less exciting environment for the subjects. This could be resolved by a similar study with subjects originating in two countries.

The lack of adverse side effects in subjects taking

melatonin suggests that it is well tolerated at the dose used. The present study, however, does not indicate whether it is necessary to take melatonin before and during the flight or only after it. Further research is needed on the dose response characteristics of melatonin to optimise its effect in alleviating jet lag.

Overall the results support the use of melatonin for alleviating jet lag and tiredness after long haul flights and indicate further investigations necessary to maximise the positive effects of melatonin.

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Observer variation in histopathological diagnosis and grading of cervical intraepithelial neoplasia

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Abstract

To assess the variability among histopathologists in diagnosing and grading cervical intraepithelial neoplasia eight experienced histopathologists based at different hospitals examined the same set of 100 consecutive colposcopic cervical biopsy specimens and assigned them into one of six diagnostic categories. These were normal squamous epithelium, non-neoplastic squamous proliferations, cervical intraepithelial neoplasia grades I, II, and III, and other. The histopathologists were given currently accepted criteria for diagnosing and grading cervical intraepithelial neoplasia and asked to mark their degree of confidence about their decision on a visual linear analogue scale provided. The degree of agreement between the histopathologists was characterised by kappa statistics, which showed an overall poor agreement (unweighted kappa 0·358). Agreement between observers was excellent for invasive lesions, moderately good for cervical intraepithelial neoplasia grade III, and poor for cervical intraepithelial neoplasia grades I and II (unweighted kappa 0·832, 0·496, 0·172, and 0·175, respectively); the kappa value for all grades of cervical intraepithelial neoplasia taken together was 0·660. The most important source of disagreement lay in the distinction of reactive squamous proliferations from cervical intraepithelial neoplasia grade I. The histopathologists were confident in diagnosing cervical intraepithelial neoplasia grade III and invasive carcinoma (other) but not as confident in diagnosing cervical intraepithelial neoplasia grades I and II and glandular atypia (other).

Experienced histopathologists show considerable interobserver variability in grading cervical intraepithelial neoplasia and more importantly in distinguishing between reactive squamous proliferations and cervical intraepithelial neoplasia grade I. It is suggested that the three grade division of cervical intraepithelial neoplasia should be abandoned and a borderline category introduced that entails follow up without treatment.

Introduction

Cervical intraepithelial neoplasia is the name given to a range of squamous epithelial abnormalities of the cervix uteri that are associated with an increased risk of subsequent invasive carcinoma of the cervix. In current histopathological practice lesions are graded according to the degree of differentiation as cervical intraepithelial neoplasia grade I, II, or III. Cervical intraepithelial neoplasia grade I represents the best differentiated lesions, previously categorised as mild dysplasia, and grade III the poorly differentiated lesions corresponding in the old terminology to severe dysplasia or carcinoma in situ. Cervical intraepithelial neoplasia grade II is the intermediate category equivalent to moderate dysplasia. The morphological criteria used in the diagnosis and grading of lesions have been reviewed by Buckley *et al.*[1]

Implicit in the nomenclature of cervical intraepithelial neoplasia is the concept of tumour progression and progressive loss of differentiation with increasing malignancy, which fits in well with the current understanding of the biology of carcinogenesis. It is presumed that at least some cases of cervical intraepithelial neoplasia grade I will eventually progress, probably through the higher grades of cervical intraepithelial neoplasia, to invasive carcinoma. Generally, cervical intraepithelial neoplasia grade I will probably take longer to progress to invasive carcinoma than a grade III lesion,[2] but forecasting the probable rate of progression is impossible in individual cases. The size of the lesion is considered to be a more important prognostic indicator than its histological grading. Therefore, the Ninth Study Group of the Royal College of Obstetricians and Gynaecologists has recommended that all cervical intraepithelial neoplasia should be regarded as a continuum and that cervical intraepithelial neoplasia grade I should be treated as seriously as grade III lesions.[3] Hence the diagnosis of cervical intraepithelial neoplasia of any grade may have serious treatment implications for the patient.

This study was designed to test the ability of histopathologists to distinguish consistently between cervical intraepithelial neoplasia and the reactive proliferations of cervical squamous epithelium and to assess the variability of grading of cervical intraepithelial neoplasia among different histopathologists. A further study designed to test the degree of intraobserver variation is currently in progress.

Materials and methods

A total of 100 consecutive colposcopic biopsy specimens of the cervix—excluding those with a computer code indicating invasive carcinoma—that were received by the histopathology department at the University Hospital of Wales between 12 November