SHORT REPORTS

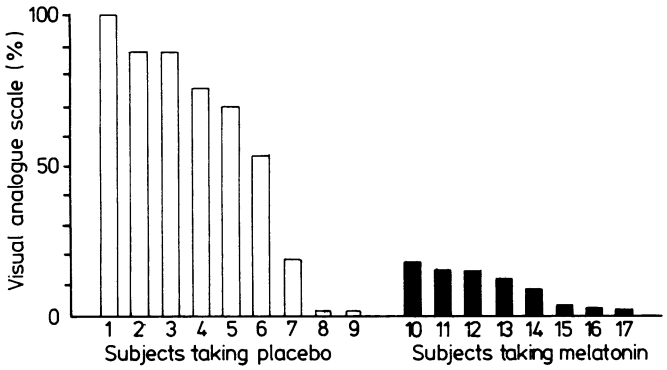
Alleviation of jet lag by melatonin: preliminary results of controlled double blind trial

Jet lag is an ill defined phenomenon resulting from rapid flight across several time zones.[1] It is considered to be due to desynchronisation of circadian rhythms, such as the sleep-wake cycle, with local time and to lack of sleep.[1] A means of rapidly resynchronising body rhythms to local time would benefit people who suffer badly from jet lag.

Various remedies for alleviating jet lag have been proposed: manipulation of dietary intake and, more recently, appropriate exposure to bright light have been used, though both are time consuming.[2,3] We previously suggested that melatonin, a methoxyindole secreted by the pineal gland, might be simpler and more effective in treating jet lag.[4] In view of its resynchronising properties in animals,[5] its ability to transduce light-dark information, its hypnotic effects in man, and its low toxicity we examined whether it helped people adapt to new time zones.

Subjects, methods, and results

Seventeen healthy volunteers (10 women and seven men aged 29-68) were recruited from the university staff and their families. All gave their informed consent to the study, which was authorised by the University of Surrey ethical committee. The subjects flew from London to San Francisco (eight time zones west), where they remained for 14 days so that they had adapted to local time before their return home. Flights were organised between 20 November 1985 and 25 January 1986.



Visual analogue scores (0=insignificant, 100=very bad) showing severity of jet lag among eight subjects given melatonin and nine subjects given placebo.

Subjects wore wrist meters (provided by Professor A Borbely, University of Zurich) for roughly one week before and 33 days after departure to continuously monitor activity. For two days before departure and on days 1-7, 14, 15, 21, and 22 after their return each subject collected six hourly sequential urine samples, kept a daily sleep log, and recorded their mood and oral temperature every two hours from 0800 or awaking, whichever was the later, until 2400 or bedtime, whichever was earlier. They also performed logical reasoning and letter cancellation tests every four hours from 0800 to 2400 on the days specified above. The results of the psychological test and hormone analyses will be reported later.

For three days before their return flight the subjects took a daily dose of melatonin (5 mg in gelatin lactose) or placebo at 1800 (local time). On their return to Britain they continued taking the same preparation at 2200-2400 (local time) for a further four days. On day 7 after arriving home the subjects were asked to rate their jet lag on a 10 cm visual analogue scale from 0 (insignificant) to 100 (very bad). Jet lag was deliberately not defined as its nature and severity vary from person to person but it was considered to be present at scores of 50 or above.

The study design was double blind and was decoded only when all data collections were complete.

Six of the nine subjects who took placebo rated their jet lag greater than 50 on the visual analogue scale (figure). None of the eight subjects who took melatonin rated their jet lag at more than 17. Fisher's exact test for small sample sizes indicated that jet lag was significantly less severe among subjects treated with melatonin ($p=0.009$).

Comment

None of the subjects taking melatonin had appreciable jet lag, whereas six of the nine treated with placebo did. It is not unreasonable that two of the subjects treated with placebo rated their jet lag as insignificant as this is consistent with the highly variable nature of the condition. It is, however, remarkable that no subject treated with melatonin was affected to any degree.

These preliminary findings must clearly be extended to much larger numbers of subjects, westward as well as eastward flight, different numbers of time zones crossed, and different times of the year. The dose of melatonin was chosen after preliminary studies but might well be optimised further; slow release preparations may be better. Nevertheless, we conclude in this limited study that melatonin does indeed alleviate jet lag.

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These preliminary findings were presented at the Chronopharmacology Meeting, Montreux, March 1986.

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Carbamazepine neurotoxicity precipitated by diltiazem

Calcium antagonists are widely used in cardiovascular and other diseases. Recent evidence suggests that they might be effective as adjunctive anticonvulsants, possibly by inhibiting propagation of seizures.[1] Their therapeutic potential would be lessened, however, if appreciable pharmacokinetic interaction occurred with anticonvulsants already in use. We report on a patient in whom administration of diltiazem but not nifedipine precipitated carbamazepine neurotoxicity.

Case report

A 34 year old man with refractory epilepsy was first assessed at this unit in March 1982. Complex partial and secondary generalised seizures, thought to be a consequence of injury at birth, had developed seven years previously. He was not intellectually impaired, and neurological assessment showed only left sided hyper-reflexia and general clumsiness. An electroencephalogram showed excess intermediate slow wave activity bilaterally. A computed tomogram of the brain was normal. Treatment with phenytoin had caused considerable sedation, sodium valproate had been blamed for an episode of pancreatitis in November 1981, and sulthiame did not reduce the frequency of seizures. Carbamazepine was introduced in February 1984 and gradually increased to a total daily dose of 1000 mg by November. Despite circulating steady state carbamazepine concentrations of 12-13 mg/l (target range 8-12 mg/l) and no clinical symptoms or signs of toxicity he continued to have as many as four complex partial seizures daily.

In March 1985 he gave written informed consent to a trial, approved by the local ethical committee, of calcium antagonist agents as adjunctive anticonvulsants. He was initially treated with verapamil 120 mg three times daily but in common with other patients developed signs of carbamazepine intoxication.[2] In May he was admitted to this hospital to determine his tolerance to two further calcium antagonists, diltiazem and nifedipine. Steady state carbamazepine concentrations of 12-13 mg/l were consistent with outpatient values, confirming good compliance. Diltiazem 60 mg three times daily was administered together with his usual regimen of carbamazepine (400 mg in the morning, 600 mg in the