

SHORT REPORTS

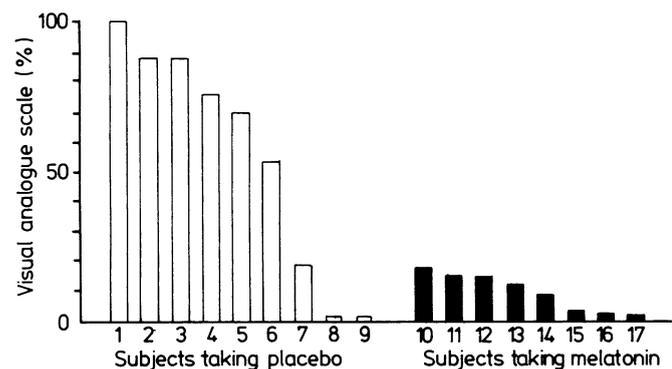
Alleviation of jet lag by melatonin: preliminary results of controlled double blind trial

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.

We thank Professor A Borbely, University of Zurich, Dr S Folkard, University of Sussex, and Dr Dennis Jones of Horner Ltd, Montreal, for advice and help; Horner Ltd, Montreal, for substantial financial support; British Caledonian Airways for free flights; Grand-Metropolitan Hotels for free accommodation; and Hogg-Robinson (travel agents) for efficiency and help in arranging the travel. Thanks also to Nabisco brands and many others who gave generous support. We also thank all our volunteers.

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

- 1 Arendt J, Marks V. Physiological changes underlying jet-lag. *Br Med J* 1982;284:144-6.
- 2 Ehret CF, Scanlon LW. *Overcoming jet-lag*. New York: Berkely Books, 1983.
- 3 Daan S, Lewy AJ. Scheduled exposure to daylight: a potential strategy to reduce jet-lag following transmeridian flight. *Psychopharmacol Bull* 1984;20:566-8.
- 4 Arendt J, Marks V. Can melatonin alleviate jet-lag? *Br Med J* 1983;287:426.
- 5 Redman J, Armstrong S, Ng KT. Free-running activity rhythms in the rat: entrainment by melatonin. *Science* 1983;219:1089-91.

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Carbamazepine neurotoxicity precipitated by diltiazem

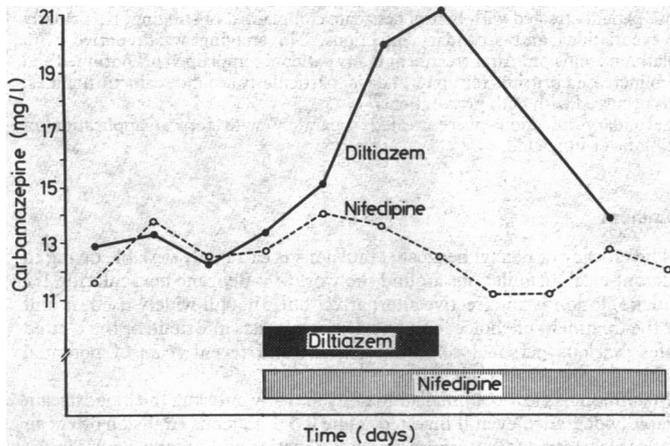
Calcium antagonists are widely used in cardiovascular and other diseases. Recent evidence suggests that they might be effective as adjunctive anticonvulsants, possibly by inhibiting propagation of seizures.¹ Their therapeutic potential would be lessened, however, if appreciable pharmacokinetic interaction 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

evening). Blood pressure was monitored throughout, and he was instructed to report any adverse effects. Concentrations of carbamazepine were determined in duplicate by enzyme immunoassay (EMIT, Syva, Palo Alto) six hours after each morning dose. Over the next 48 hours he complained of dizziness, nausea, ataxia, and diplopia, consistent with carbamazepine neurotoxicity. Plasma carbamazepine concentrations showed a concurrent rise to a peak of 21 mg/l, 40% higher than baseline values (figure). Stopping diltiazem was associated with a corresponding decrease in carbamazepine concentrations to previous values. The neurotoxic symptoms rapidly resolved. Blood pressure remained unaltered during treatment.



Carbamazepine concentrations during concomitant treatment with diltiazem 60 mg three times daily or nifedipine 20 mg three times daily.

Three months later he was readmitted and nifedipine 20 mg three times daily was administered. No adverse effects were reported, and circulating carbamazepine concentrations were unaffected (figure). He continued to take nifedipine and carbamazepine and noted a substantial subjective improvement in control of seizures.

Comment

Both carbamazepine and diltiazem are lipid soluble drugs that are eliminated primarily by hepatic metabolic processes. The most likely mechanism of interaction is inhibition of metabolism of carbamazepine by diltiazem. This is strongly supported by a recent study in mice in which both diltiazem and verapamil inhibited hepatic mono-oxygenase activity, probably by binding to cytochrome P450.³ As carbamazepine has the unusual property of inducing its own metabolism an inhibitory interaction is likely to produce a greater than expected increase in circulating carbamazepine concentration.⁴ The potential of diltiazem to inhibit the metabolism of other lipid soluble agents merits further investigation. Though nifedipine also undergoes hepatic metabolism, it belongs to a subgroup of calcium antagonists functionally and structurally dissimilar to diltiazem and verapamil and shows different receptor specificity.⁵

New anticonvulsants with fewer sedative side effects are urgently required, but traditional add on methods of assessment are inappropriate when pharmacokinetic interaction occurs with existing drugs. Such interaction seems to occur with verapamil and diltiazem but not with the dihydropyridine nifedipine.

- Overweg J, Binne CD, Meijer JWA, *et al*. Double-blind placebo controlled trial of flunarizine as add-on therapy in epilepsy. *Epilepsia* 1984;25:217-22.
- Macphee GJA, McInnes GT, Thompson GG, Brodie MJ. Verapamil potentiates carbamazepine neurotoxicity: a clinically important inhibitory interaction. *Lancet* 1986;i:700-3.
- Renton KW. Inhibition of hepatic microsomal drug metabolism by the calcium channel blockers diltiazem and verapamil. *Biochem Pharmacol* 1985;34:2549-53.
- Macphee GJA, Brodie MJ. Carbamazepine substitution in severe partial epilepsy: implication of autoinduction of metabolism. *Postgrad Med J* 1985;61:779-83.
- Snyder SH, Reynolds IJ. Calcium-antagonist drugs: receptor interactions that clarify therapeutic effects. *N Engl J Med* 1985;33:975-1002.

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Spontaneous remission and relapse in adult T cell lymphoma/leukaemia associated with HTLV-I

Adult T cell lymphoma/leukaemia¹ associated with human T lymphotropic virus type I (HTLV-I) is usually a rapidly progressive disorder. We describe a patient who presented with a lymphomatous skin infiltrate which underwent spontaneous remission. Five years later he developed classic adult T cell lymphoma/leukaemia.

Case report

In 1980 a 41 year old motor mechanic (who had been born in Grenada but had lived in London for 21 years) presented with a generalised papular rash, arthralgia, and mild conjunctivitis. The rash comprised small discrete 1-2 mm raised papules without erythema, scaling, or itching. It affected the extensor surfaces of his arms and legs. A biopsy specimen of a lesion showed a dermal and epidermal infiltrate of large mononuclear cells, and the condition was thought to be sarcoidosis. The patient failed to attend for a Kveim test or for follow up as the rash resolved within six months without treatment.

In May 1985 he returned with pyelonephritis and obstruction of the right pelviureteric junction. An elective pyeloplasty was performed. The peripheral blood was normal. Six weeks later he returned with a rash similar to that noted in 1980, together with fever, arthralgia, and pronounced conjunctivitis. The lesions affected predominantly ear lobes, face, lips, arms, and legs. His trunk was relatively spared as were flexor surfaces. The hands (figure) and feet were affected, including the palms and soles. There was no lymphadenopathy but hepatosplenomegaly was noted. There were no neurological or mucous membrane lesions.



Papular appearance of lymphomatous skin infiltrate.

The results of investigations included an abnormal white cell count of $18.9 \times 10^9/l$ with 60% lymphocytes, most of which were abnormal with lobed nuclei and prominent nucleoli. Urea, creatinine, electrolyte, and calcium concentrations were normal. Liver function tests gave normal results except for a raised alkaline phosphatase activity. A skin biopsy specimen confirmed infiltration of the dermis and epidermis by large lymphocytes suggestive of lymphoma. On review the 1980 appearances were morphologically identical. Immunohistochemistry showed T lymphocytes of the T4 (T helper) phenotype. Cell surface marker studies on the peripheral blood mononuclear cells gave the following results: pan T cell 87%; T4 96% and T8 (T suppressor) 3%; T cell activation antigen 72%; pan B cell 1%. The bone marrow was infiltrated by lymphoma. Antibody to HTLV-I was detected in serum by an enzyme linked immunosorbent assay, supporting a diagnosis of adult T cell lymphoma/leukaemia.

In view of the history and normal calcium concentration no cytotoxic chemotherapy was given. Two weeks later, because of worsening arthralgia and a rising calcium value, treatment was started with α interferon, followed by three cycles of combination chemotherapy with methotrexate, bleomycin, doxorubicin (Adriamycin), cyclophosphamide, vincristine, and dexamethasone (M-BACOD). The hypercalcaemia improved but not the rash or the lymphocytosis, and the spleen became enlarged. A trial of 2'-deoxycoformycin was started by intravenous injection. This preparation inhibits adenosine deaminase and is cytotoxic in some malignancies arising from T lymphocytes,² including adult T cell lymphoma/leukaemia.³ A steady response was seen with deoxycoformycin, total dose 30 mg/m² given over five weeks. The rash resolved, the abnormal lymphocytes cleared from the peripheral blood, the spleen became impalpable, and the calcium concentration remained normal. Toxicity included transient increases in urea, creatinine, and transaminase values. Cytopenias were complicated by recurrent fungal infection.