RESEARCH

Management of Dyschronosis (Jet Lag) a preliminary study

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Jet lag or circadian desynchronisation develops after a Longditudinal journey involving two or more time zones, during which biological rhythms decouple as a result of confusing internal and external cues. The stresses induced by this, overlaid by a number of other stresses such as the effects of lowered cabin pressure, deoxygenation and the muscle damage associated with prolonged inactivity combine to produce the distinctive jet lag effect.

Stokes and Kite (1997)[1] demonstrated that two different synchronisations were disrupted in dyschronosis. The first is at the interface between the body's internal rhythms and the external environment, and the second on desynchronisation of the various internal rhythms between each other.

The principal influence on the synchrony with the external environment is the diurnal light/darkness cycle. Internal cycles are influenced by feeding times and the interplay of various digestive organs and also by hormonal cycles, temperature cycles and activity. It is generally accepted that it takes about one day for each time zone crossed for body temperature to re-adapt to the new environmental cues[2] .

The direction of travel affects the severity of jet lag. Flying in a westward direction is generally less traumatic. This is because extending the circadian cycle ahead of the sun seems less stressful to the various internal cycles than *vice versa*.

Modifying the Physiology of Jet Lag

The pathophysiology of dyschronosis is not yet completely understood. However hormones such as melatonin and cortisol, which have a natural circadian cycle are believed to play a significant role in circadian homeostasis.[3,4]. Jet lag is a summation of a number of stress effects and so the production of cortisol would be expected as part of the standard stress response. Melatonin, secreted by the pineal gland, is under light control. It had been anticipated that melatonin would be of value in preventing jet lag but trial results have been variable and research by Buscemi, and colleagues[5] has indicated that in clinical situations, melatonin has limited value either in assisting with the jet lag *per se* or merely inducing sleep. In addition although generally a very safe drug, there are some concerns following reports of interactions between melatonin and warfarin and of fits in younger individuals[6,7].

Since light is the major factor in setting the circadian body clock, manipulation of light to reset or re-integrate the cycles quickly after dyschronosis has been shown to have value[8]. Airlines encourage use of such light reprogramming; indeed British Airways even supplies an on-line calculator for passengers to design their own light exposure programme. While this is of some value it is only palliative and the routines of waking and exposing to bright light in the middle of the night, which is sometimes necessary for the system to work, limits its usefulness.

There are other more complex programmes involving fasting as well as light manipulation but these are not widely used. There are also various homeopathic remedies widely advertised but with no indication of ingredients. These and other methods involving 'grounding the electromagnetic system by standing barefoot in bright light without wearing glasses', pressing pressure points on the body at regular intervals during the flight or applying bright lights behind the knees for a period after a flight, although widely marketed, suggest at best a placebo effect and there are no proper tests for efficacy or explanations of a mode of action.

The effects of jet lag on individuals are variable. They include disruption of sleep, gastrointestinal disturbances, decreased vigilance, lack of arousal, and lack of energy[9]. Cognitive effects are often marked. Individuals report inability to type accurately, driving concerns, and "zombie-like" behaviour as well as anxiety, irritability and depression[10].

Cho, et al., (2000)[10] have reported that flight crew suffering from chronic jet lag have higher concentrations of stress hormones and smaller temporal lobes or centres of short-term memory in the brain, than those that fly short-haul with regular shift patterns.

It is not known whether the altered brain structure and function is permanent but they suggest longer recovery times built into flight rosters should be considered.

It is important to bear in mind that daylight related cycles are not the only factors affecting the severity of jet lag. Stress and fatigue associated with the period pre-travelling, as well as the aviation aspects such as low cabin pressure, reduced oxygen levels and muscular inactivity limiting lymphatic and venous return, all exacerbate the primary desynchronisation[11]. They also however also affect the interplay of the many internal cycles which would appear to play a much more significant role than previously appreciated. It is the disruption of these cycles which mean that even a totally blind person with no concept of daylight will still suffer from jet lag.

An important aspect of recent research by Kornmann and co-workers[12] in relation to this was the finding that a heat shock protein stimulating factor (HSF1) plays a significant role in signalling dyschronosis to the internal stress management sys-

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tem and initiating the production of heat shock proteins (HSP's) which appear to play a very significant role in bringing the peripheral clocks back into synchrony.

Heat Shock Protein Significance

The importance of heat shock proteins in all pathophysiological process has only recently become recognised. Also known as chaperones or stress proteins, heat shock proteins (HSPs) are a series of intracellular proteins of varying sizes up to 100kDa which are highly conserved across the entire plant and animal kingdoms[13]. They were only recognised for the first time in humans in 1988[14]. They have numerous functions within the cell but particularly they are involved in ensuring proper folding and transportation of cell proteins and the maintenance of cell membranes and their repair when damaged. When an individual is stressed, there is an immediate requirement for increased levels of HSPs to allow the repair of even the most minor organelle damage to proceed. Following any physical stress the damaged cells release a heat shock-stimulating factor (HSF1 or HSF2) and chaperone (HSP) production becomes a priority. Older people produce HSP's more slowly and thus recovery from physical stress is more prolonged in the older subject. (For review of HSP function in all animals see Morimoto & Santoro1998[15].)

The demonstration by Kornmann *et al*. of a role for HSP's in management of desynchronisation[12] has helped to explain the recently demonstrated effect of the heat shock protein factor (HSF1) derived from prickly pear skin on jet-lag. 'Protex-H®', a registered food supplement derived from a concentrated extract of the skin of the prickly pear (*Opuntia* spp) was originally approved as a food supplement by the European Union (EU) for use in stress management in commercial scuba divers but is now also widely used as an approved supplement for management of stressors in animal husbandry.

The concentrated extract is presented in a readily absorbed tablet form. Published peer-reviewed research has shown that small amounts in the diet allow the vertebrate body to induce HSP's much more rapidly after any stress and results can be remarkable,[16,17,18,19].

Research volunteers from among a group of international medical and veterinary scientists have recently carried out trials involving taking the prickly pear extract two hours prior to long haul flights, across 5 or more time zones. Fourteen scientists were involved, 11 male and three female, aged forty years or over. All were seasoned travellers used to the effects of jet- lag, and initially sceptical of the likely benefit of a cactus fruit extract on an intractable problem.

The study involved flights from UK to Western US, Chile, New Zealand, Australia, and Western Canada or from Eastern US to India, S.E Asia and China. Each was advised on how to take the supplement and asked to report on level of tiredness, co-ordination difficulty and awareness typifying effects of jet lag on the first two days after arrival.

Results have been encouraging and justify further work on the product. Virtually all users, familiar with the effects of jet lag, considered it to have removed most, or all of the symptoms. Apart from normal tiredness, only occurring if they had been unable to sleep on the plane, they all reported significant improvement in their anticipated tiredness and cognition difficulty at arrival. Those proceeding to meetings or lecture commitments considered that they had been able to assume a normal operational capacity immediately. It was difficult, once they had perceived benefit, to ensure they acted as controls for the return flight.

In Fig 1, the bar chart shows the results to date of this study, which continues. Currently the trial has involved over 100 trans-meridian journeys, each crossing at least five time zones. These are broken down into East West and West East flights both with and without the use of the extract at recommended levels.

As can be seen, with very few exceptions the test set of travellers experienced considerable relief from the effects of jet lag if they took the extract before the flight. The reason for the smaller number controls travelling without the extract was that, where users had experienced the benefits on a flight when outward bound, they were reluctant to omit it for the return flight.

Regular users of 'Protex H®' for jet lag include medical professionals, businessmen, professional and amateur athletes. This trial demonstrates that the supplement, justifies a double blind placebo controlled testing to confirm potential value in combating jet lag.

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Interest declared involvement in development of Protex H® for management of jet lag, and is with Braden Ltd, the distributor.

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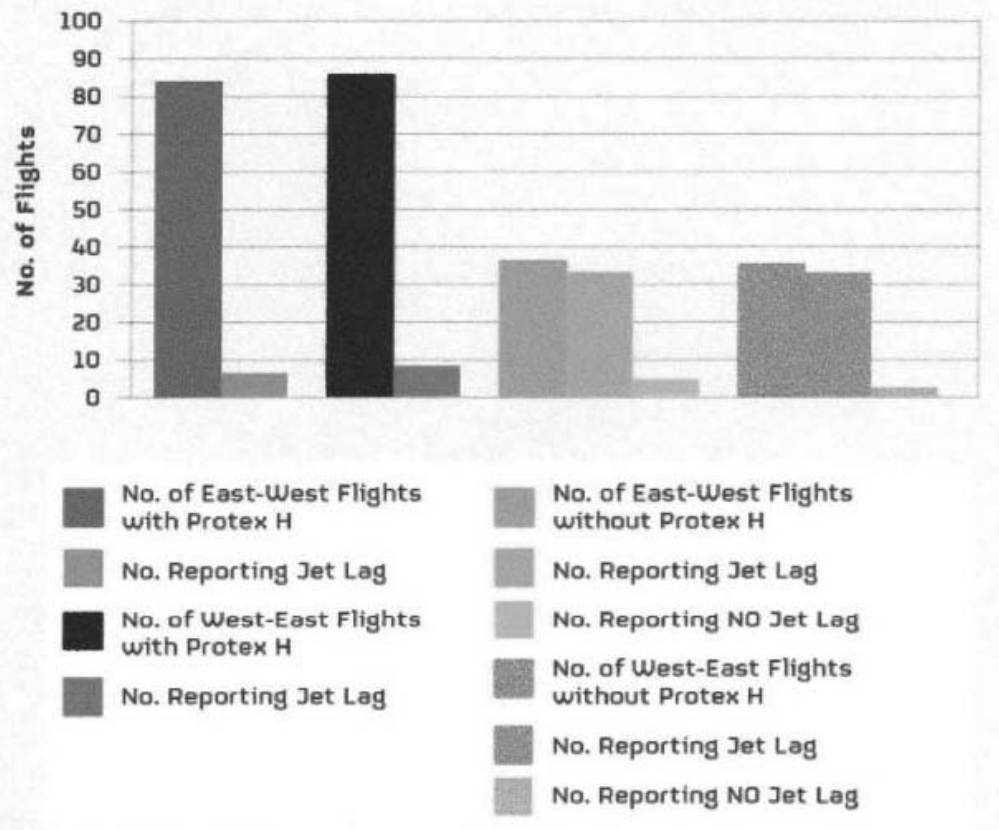
Figure 1 – Effect of Protex-H on Jet Lag



The graph above shows the results for over 100 trans-meridian journeys, from the UK to countries including the USA, Canada, Chile Thailand, Singapore and Australia. These are broken down into East West and East flights both with and without the use of Protex-H at recommended levels. All were regular travellers and were very familiar with the effects of jet lag on their body after such journeys.