Clinical update: melatonin and sleep disorders

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ABSTRACT – The hormone melatonin is increasingly used for the treatment of certain sleep disorders, particularly those related to disturbed biological rhythms. This article summarises current knowledge of its mechanism of action and identifies situations where there is good evidence for its efficacy. The authors provide advice, based on their own experience and consistent published data, concerning the dose range of melatonin to be used and the critically important question of the timing of treatment. Anecdotal evidence for the use of melatonin needs to be replaced by data from well-controlled, preferably multi-centre, randomised clinical trials.

KEY WORDS: blindness, children, circadian rhythm, elderly, jet lag, melatonin, neurodisability, shift work, sleep

Introduction

Despite its controversial past, melatonin has been and continues to be used by healthcare professionals to treat certain sleep disorders.[1] There is growing clinical evidence to support the use of melatonin within specific groups of patients with problems related to sleep timing and consolidation, such as the blind, delayed sleep-phase syndrome (DSPS) patients, the elderly, children with neurodisabilities and other sleep disorders. A meeting held in 2007 at the Royal Society of Medicine brought together over 56 healthcare professionals with an interest in sleep disorders to discuss the current use of melatonin in Europe. It became clear that most of the delegates were attending to seek a greater understanding of melatonin and guidance on its use, despite the fact that the majority were currently prescribing the drug. The use of melatonin is frequently based on anecdotal evidence or small clinical trials and there is little uniformity in the doses and formulations being used (at least 40 preparations are available across Europe, the vast majority of which are non-pharmaceutical grade material). The conclusion from the meeting was that clear guidelines for melatonin use are required and there is a need for clarification of the dose, formulation and timing of melatonin administration. The effects, or absence of effects, that can be expected within specific groups of patients in different therapeutic conditions need to be specified so that the true therapeutic potential can be assessed.

It is estimated that there are over 80 sleep disorders and approximately 30% of the adult population will experience problems with initiating or maintaining sleep in any one year.[2,3] Children with neurodisabilities and severe visual impairment also frequently suffer from disturbed sleep, as do their families. Sleep disorders therefore pose a significant individual but also public health problem, particularly in those patients with a long-term sleep disorder most commonly treated with hypnotics, including benzodiazepines and non-benzodiazepines. These drugs, however, have the potential to induce addiction, cause withdrawal symptoms or trigger rebound insomnia and have other adverse effects that increase with advancing age.[4]

Mechanism of action of melatonin

Melatonin is a chronobiotic, a hormone that adjusts the timing of the central biological clock, including the timing of the sleep-wake cycle.[5,6] During the daytime hours exogenous melatonin lowers core body temperature and increases sleep propensity. Melatonin is normally secreted during darkness and the endogenous hormone serves to reinforce 'darkness physiology'. Levels begin to rise in the evening, with peak concentrations being reached between 02:00 and 04:00 in adults. Mistimed (or, in some reports, lowered) melatonin production is associated with chronic or intermittent disturbances in sleep onset and/or duration. Providing a suitably timed exogenous source of melatonin can assist in realigning the sleep-wake cycle and restore sleep patterns.[6,7]

Efficacy, dose and timing of treatment

There is no doubt that the prescribing of melatonin is continuing to increase despite a poor scientific base, and with no consistent guidance on the dose and when it should be given. This has been recognised by the NHS which is funding at least one national randomised controlled trial in children with neurodevelopmental delay and impaired sleep, which commenced in late 2007 and with results expected in late 2009.

Limited clinical trials to date have shown that

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Clin Med 2008;8:381–3

melatonin positively improves sleep disturbances in blind patients and in DSPS in adults.[6,7,8] Some, but not all reports have shown positive effects on sleep disturbances in the elderly.[9,10] Positive effects on sleep have also been found in very old and demented elderly, although potential adverse effects on mood may limit its use to low doses or use in combination with bright light.[11] Melatonin is also recognised to be helpful in individuals suffering the effects of shift work and jet lag.[12,13] In field studies on shift workers the application of melatonin to improve alertness and sleep has had some modest success,[14] but much still remains to be understood. The use of melatonin to treat jet lag has provided some inconsistent results but most studies report beneficial effects when the dose is correctly timed.[12,13] There is little evidence for its efficacy when the appropriate timing of treatment is unpredictable, for example after short stopovers.

Additionally, a significant decrease in time to sleep onset occurs in children with neurodisabilities,[15] and more recently in healthy and attention-deficit/hyperactivity disorder children with idiopathic chronic sleep onset insomnia and with phase-delayed melatonin production.[16]

Table 1 outlines the doses of melatonin for sleep disorders in various groups of subjects as presently advised by the authors. No particular formulation is specified since there are very few comparative data.

Recent meta-analyses have disagreed regarding the therapeutic benefits of melatonin,[9,17,18] and the conclusions of Buscemi *et al*[18] have been disputed.[19,20] The most likely reason for inconsistent results particularly in field studies, is that melatonin treatment was incorrectly timed. This point is not fully appreciated. If a phase advance is required and treatment is timed to delay the internal clock, for example, the opposite of the desired result may be obtained. The large differences in individual response to, for example, night shift or jet lag, mean that timing treatment is difficult unless internal clock timing is known.[5,12] A consensus does exist, however, that melatonin is a safe treatment with appropriate dosage and timing.[9,17,18,10,21]

Table 1. Doses of melatonin for sleep disorders in various groups of subjects as presently advised by the authors.

Indication	Suggested dose (mg)	Timing of dose
Elderly and demented elderly	0.5	Long-term repeated daily intake at a regular, fixed time of day, just before habitual bedtime
Jet lag	0.5–5	Requires specific instructions depending on circadian status, flight details and number of time zones crossed
Blind	0.1–5	For non-24 hour sleep–wake cycle disorder, initial timing to advance the internal clock, after realignment,
maintenance		timing just before normal bedtime. Treatment started in a 'good' sleep phase, just before normal bedtime is usually successful
Delayed sleep-phase syndrome	0.5–5	Initial timing to advance the internal clock (usually late afternoon/early evening), after realignment, maintenance timing just before normal bedtime
Children with neurodisabilities	0.5–12	20–30 min before normal bedtime

Conclusions

There is only limited clinical evidence and a growing tranche of anecdotal evidence on the use of melatonin to date. Clear guidelines are required for the use of melatonin in each of the key therapeutic areas based on clinical evidence and a defined melatonin formulation. In addition, to clarify the indications and expectations of prescriptions, a collaborative effort of clinicians and researchers is clearly indicated to replace anecdotal evidence with robust, well-controlled and, almost certainly, multi-centre, randomised clinical trials.

Acknowledgements

This article has been compiled following a discussion meeting sponsored by Alliance Pharmaceuticals Ltd.

Competing interests

JA is a consultant to Alliance Pharmaceuticals, and a director and shareholder of Stockgrand Ltd, a company that measures melatonin and other hormones. DS is a director and shareholder of Stockgrand Ltd, a company that measures melatonin and other hormones. RA is a co-principal investigator of a randomised controlled trial funded by the NHS Health Technology Assessment Programme and which is being undertaken in collaboration with Alliance Pharmaceuticals Ltd. TA and EvS have no competing interests

References

1 Turek FW. Melatonin hype hard to swallow. *Nature* 1996;379:295–6.
2 American Academy of Sleep Medicine. *The international classification of sleep disorders: diagnostic and coding manual*. Westchester, IL: AASM, 1990.
3 Addison RG, Thorpy MJ, Roehrs TA, Roth T. Sleep/wake complaints in the general population. *Sleep Res* 1991;20:112.
4 Van Someren EJW. Circadian and sleep disturbances in the elderly. *Exp Gerontol* 2000;35:1229–37.
5 Arendt J. Melatonin: characteristics, concerns, and prospects. *J Biol Rhythms* 2005;20:291–303.
6 Arendt J, Skene DJ. Melatonin as a chronobiotic. *Sleep Med Rev* 2005;9:25–39.
7 Lockley SW, Skene DJ, James K *et al*. Melatonin administration can entrain the free running circadian system of blind subjects. *J Endocrinol* 2000;164:R1–6.
8 Skene DJ, Arendt J. Circadian rhythm sleep disorders in the blind and their treatment with melatonin. *Sleep Med* 2007;8:651–5.
9 Brzezinski A, Vangel MG, Wurtman RJ *et al*. Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Med Rev* 2005;9:41–50.

10 Riemersma RF, Mattheij CAM, Swaab DF, Van Someren EJW. Melatonin rhythms, melatonin supplementation and sleep in old age. In: Straub RH, Mocchegiani E (eds), *The neuroendocrine immune network in ageing*. Amsterdam: Elsevier, 2004:195–211.
11 Riemersma-van der Lek R, Swaab DF, Twisk J *et al.* Effect of bright light and melatonin on cognitive and non-cognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA* 2008;299:2642–55.
12 Arendt J, Stone B, Skene D. Sleep disruption in jet lag and other circadian rhythm disturbances. In: Kryger M, Roth T, Dement W *et al* (eds), *Principles and practice of sleep medicine*, 4th edn. Philadelphia: Elsevier, 2005:659–72.
13 Waterhouse J, Reilly T, Atkinson G, Edwards B. Jet lag: trends and coping strategies. *Lancet* 2007;369:1117–29.
14 Bjorvatn B, Stangenes K, Oyane N *et al.* A randomized placebo-controlled field study of the effects of bright light and melatonin for adaptation to night work. *Scand J Work Environ Health* 2007;33: 204–15.
15 Phillips L, Appleton RE. Systematic review of melatonin treatment in children with neurodevelopmental disabilities and sleep impairment. *Dev Med Child Neurol* 2004;46:771–5.
16 Van Der Heijden KB, Smits MG, Van Someren EJW, Ridderinkhof KR, Gunning WB. Effect of melatonin on sleep, behavior and cognition in ADHD and chronic sleep onset insomnia. *J Am Acad Child Adolescent Psychiatry* 2007;46:233–41.
17 Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev* 2002;CD001520.
18 Buscemi N, Vandermeer B, Hooton N *et al.* Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. *BMJ* 2006;332:385–93.
19 Arendt J. Does melatonin improve sleep? Efficacy of melatonin. *BMJ* 2006;332:550.
20 Herxheimer A. Does melatonin help people sleep? *BMJ* 2006;332: 373–4.
21 Arendt J. Safety of melatonin in long term use? *J Biol Rhythms* 1997;12:673–82.