

DRUG UPDATE

No. 44

November 2005

MELATONIN FOR SLEEP DISORDERS IN CHILDREN

Limited evidence suggests short-term use of melatonin may be effective in the treatment of sleep-onset insomnia in some children. Evidence of efficacy for other sleep disorders in children is lacking. Melatonin appears to be well tolerated during short-term use, although new or increased seizure activity has been reported. Efficacy and safety for longer than four weeks has not been evaluated and treatment should be initiated and managed by a specialist. Melatonin is not licensed for use in the UK but is available on a named patient basis.

What is it?

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone secreted by the pineal gland, located in the brain. One of its primary functions is in the regulation of circadian rhythm and sleep. Based upon its physiological role, exogenous melatonin has been used to manipulate circadian rhythm and induce sleep.¹ As a naturally occurring substance it is thought not to be associated with the adverse effects of conventional hypnotic agents.¹ Melatonin is not licensed in the UK but can be prescribed on a named patient basis.

How effective is it?

A number of small randomised controlled trials have described the use of melatonin in children with sleep disorders. Two placebo-controlled trials evaluated melatonin in the treatment of children who presented with idiopathic sleep-onset insomnia.^{2,3} Some children had previously been diagnosed with attention-deficit hyperactivity disorder (ADHD) and treated with methylphenidate; salbutamol and lactulose were the only co-medications allowed. The diagnosis of sleep disorder was sleep onset later than 8:30pm in children aged six years and for older children 15 minutes later per year until the age of twelve. Sleep latency had to be greater than 30 minutes.^{2,3} Measures to improve sleep behaviour using good bedtime routines had failed. In the first study (n=40), time of sleep-onset was measured by parental diary and wrist actigraphs over a 4-week period.² Sleep latency (time between 'lights out' and sleep-onset) was not an appropriate marker as the children were allowed to go to bed when they felt tired. A statistically significant effect on sleep-onset time (with a dose of 5mg at 6pm) was recorded (p=0.005). The mean improvement in the melatonin group compared with baseline was approximately one hour, although diary and actigraph methods did not correlate well.² A second study (n=62) used questionnaires to measure the effect of melatonin (5mg at 7pm) over four weeks on the daytime functioning of children with sleep

disorders.³ A statistically significant improvement was observed in questionnaire scores relating to general health (p= 0.013) and functional limitations (p=0.009), but the clinical importance of these findings are unclear.³

The remaining studies involved children with a variety of neurological disorders.⁴⁻⁸ Melatonin at an initial dose of 3mg, which could be titrated up to a maximum of 9 mg, was shown to be effective in improving sleep latency in 25 children and young adults with and without epilepsy.⁴ Other studies involving this group of patients showed improvements in total sleep time and quality of life (dose 6-9mg).^{5,6} Reductions in sleep latency time were also observed in children with developmental disabilities (dose 2.5-7.5 mg).^{7,8} The diagnosis of sleep disorder, concomitant medication, dosage of melatonin and time of administration in these studies all varied. In addition, the numbers of subjects included were small, such that it is difficult to assess the overall effectiveness of melatonin in this diverse group of patients.

How safe is it?

There are no controlled studies that specifically address the safety of melatonin use in children. A study using a dose of 5 mg at bedtime, initiated to investigate the effect of melatonin in six children with severe neurological disabilities, was suspended after four of the children developed increased seizure frequency (although this is only available as an abstract).⁹ Seizure frequency returned to baseline after melatonin was discontinued and a positive re-challenge confirmed the effect. In the first study described above, one child developed mild generalised epilepsy after 4 months treatment,² whilst in another, two epileptic children out of a total of eleven who were seizure free at the start of the study re-developed seizures after 4 weeks.⁴ Other studies reported no change in seizure frequency with treatment being well tolerated.^{8,10} The safety of melatonin when used for longer than four weeks is unknown.

When should it be used?

The limited available data suggest that short-term use of melatonin may be useful in children who have difficulty falling asleep at night. There is currently no convincing evidence to suggest that melatonin is helpful in the treatment of other sleep disorders. Although melatonin appears to be well tolerated in short-term studies, long-term safety has not been established. Caution should be exercised if using melatonin in children who experience seizures, or have lowered seizure threshold.

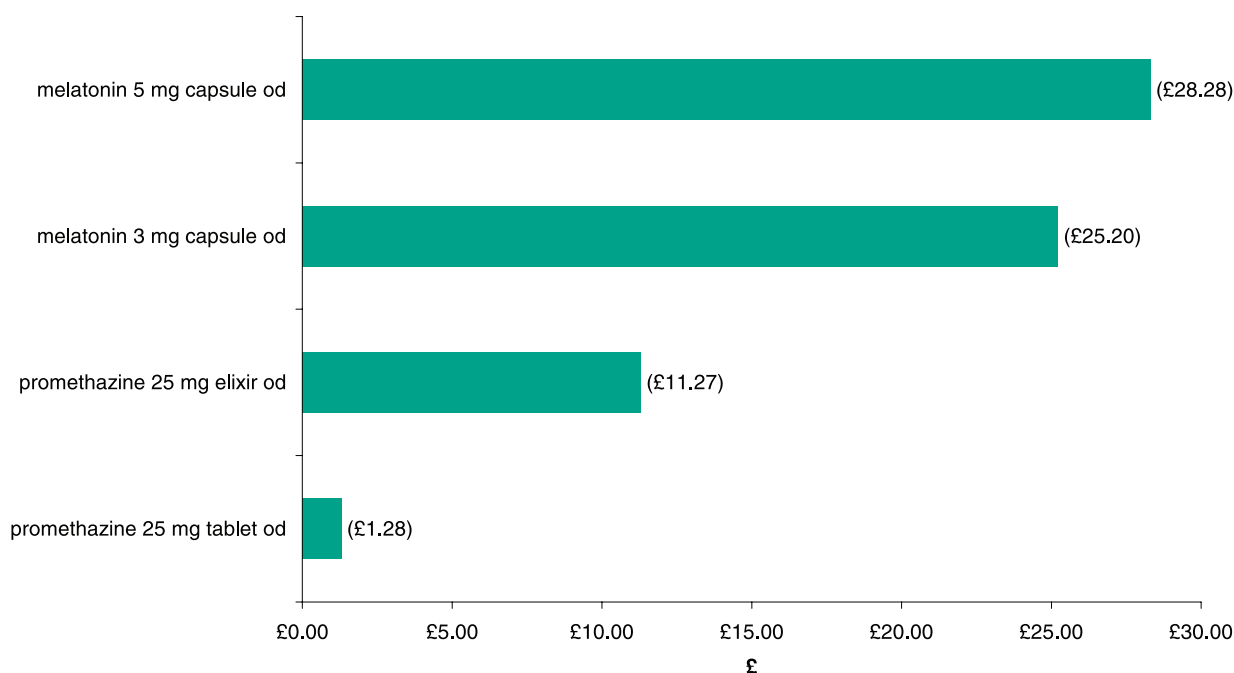
The frequency of melatonin use in primary care has increased

How much does it cost?

approximately 4-fold since 2001, in both the former Northern and Yorkshire region and in Greater Manchester Strategic Health Authority, although the numbers are still small.

Conventional hypnotic agents are not recommended for use in children for longer than a few days.¹¹ As such there are few options for the management of sleep disorders in children. The BNF for Children recommends that treatment should be initiated and managed by a specialist.¹¹ Clear arrangements regarding responsibilities for monitoring and stopping therapy should be drawn up. Where existing arrangements are demonstrated to work well they should not be dismantled.

Cost for 28 days treatment (prices from Penn Pharmaceuticals/Drug Tariff November 2005)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

REFERENCES

1. Armour D, Paton C. Melatonin in the treatment of insomnia in children and adolescents. *Psychiatr Bull R Coll Psychiatr* 2004;28:222-4 (R)
2. Smits MG et al. Melatonin for chronic sleep onset insomnia in children: A randomized placebo-controlled trial. *J Child Neurol* 2001;16:86-92 (RCT)
3. Smits MG et al. Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: A randomized placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2003;42:1286-93 (RCT)
4. Coppola G et al. Melatonin in wake-sleep disorders in children, adolescents and young adults with mental retardation with or without epilepsy: a double-blind, cross-over, placebo-controlled trial. *Brain Dev* 2004;26:373-6 (RCT)
5. Gupta M et al. Add-on melatonin improves sleep behaviour in children with epilepsy: randomized, double-blind, placebo-controlled Trial. *J Child Neurol* 2005;20:112-5 (RCT)
6. Gupta M et al. Add-on melatonin improves quality of life in epileptic children on valproate monotherapy: a randomized, double-blind, placebo-controlled trial. *Epilepsy Behav* 2004;5:316-21 (RCT)
7. McArthur AJ et al. Sleep dysfunction in Rett syndrome: a trial of exogenous melatonin treatment. *Dev Med Child Neurol* 1998;40:186-92 (RCT)
8. Dodge NN et al. Melatonin for treatment of sleep disorders in children with developmental disabilities. *J Child Neurol* 2001;16:581-4 (RCT)
9. Sheldon SH et al. Pro-convulsant effects of oral melatonin in neurologically disabled children. *Lancet* 1998;351:1254 (Abs)
10. Gupta M et al. Effects of add-on melatonin on sleep in epileptic children on carbamazepine monotherapy: A randomized placebo controlled trial. *Sleep Biol Rhythms* 2004;2:215-9 (RCT)
11. BNF for Children Sept 2005. British Medical Association, Royal Pharmaceutical Society of Great Britain, Royal College of Paediatrics and Child Health, Neonatal and Paediatric Pharmacists Group. Sub-section 4.1 Hypnotics and Anxiolytics (G)

KEY RCT - randomised controlled trial, MA-meta analysis, R-review

Regional Drug and Therapeutics Centre
Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH
Tel: 0191 232 1525 Fax 0191 261 9359 E-mail: nyrdtc.di@ncl.ac.uk
Website: www.nyrdtc.nhs.uk