

## NUTRACEUTICALS

**(8) MELATONIN**

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*Melatonin is a popular nutraceutical but it is not licensed in the United Kingdom. However, many people buy it in the United States or on the internet and pharmacists are in a good position to answer questions from their clients about this supplement*

In the past two or three years the hormone melatonin has become popular, and thousands of articles have written about it in the popular and scientific press. But it is often hard to differentiate between unproven myth and scientific fact and pharmacists are in a good position to be able to answer questions about this supplement.

**WHAT IS IT?**

Melatonin (N-acetyl-methoxytryptamine) is the primary hormone secreted by the pineal gland, a gland which lies at the centre of the brain. The hormone was first identified in the late 1950s and it is synthesised from the amino acid tryptophan, via the intermediate serotonin. The biosynthesis and release of melatonin is inhibited by exposure to light. Melatonin secretion starts as soon as darkness falls and usually peaks between 2 and 4am. Babies secrete little melatonin, but from the age of about three months melatonin concentrations begin to increase, and the concentration peaks between one and three years of age. Young adults secrete 5–25µg of melatonin daily and this amount decreases markedly with age.<sup>1</sup> The 24-hour cycle (or circadian rhythm) of melatonin secretion occurs automatically and is observed even when subjects are kept in darkness. Light seems to alter this rhythm rather than cause it.<sup>2,3</sup>

Melatonin is rapidly metabolised by the liver, with more than 85 per cent being excreted in urine as 6-sulphatoxymelatonin (6-SMT), the compound which is used in research to measure plasma melatonin.<sup>4</sup> Low doses of between 0.1mg and 0.3mg result in serum concentrations similar to the usual physiological night-time peak. However, doses of between 1 and 5mg (pharmacological doses) result in serum concentrations of up to 100 times higher

than this concentration.<sup>3</sup> Nevertheless, even doses of 50mg are quickly cleared, although after two weeks of daily dosing, lipid storage occurs.<sup>1</sup>

Since it is a hormone, melatonin has been called a drug. However, it is also a nutrient. Melatonin has been identified in bananas, tomatoes, cucumbers and beetroots,<sup>5</sup> and the consumption of plant material containing high levels of melatonin may alter serum concentrations.

**LEGAL REQUIREMENTS**

Melatonin is a good example of how different countries have different regulations. In Britain, the Medicines Control Agency has restricted melatonin to prescription, on a named-patient basis only. There are no British licensed products, so it is unlawful to promote melatonin. However in America, melatonin is freely available as a food supplement and antioxidant, and British residents can legally bring melatonin purchased in America back home for their personal use.<sup>6</sup>

**USES**

Based on its physiological roles, melatonin has been investigated for many different uses. Since it controls the circadian rhythms, it has been widely researched as an aid to jet lag and problems of insomnia. Melatonin has also been found to be a powerful free radical scavenger and as such its use as an antioxidant and in ageing has been studied. Leading on from this work, the role of melatonin in the immune system and in cancer has led to research in these areas too. Melatonin has also been found to be involved in seasonal breeding of animals and its effects on human reproduction have been studied.

**Jet lag** Jet lag is a considerable problem in the modern world with much travelling being done for both business and pleasure. When the internal body clock (or circadian rhythm) is not synchronised with the external "local" time, jet lag is experienced. The symptoms include tiredness, inability to concentrate and disturbed sleep for several days after a long flight, all of which can in-

terfere with business meetings and leisure activities. Symptoms are more marked in older travellers, and as more time zones are crossed, and tend to be worse when travelling in an easterly direction.<sup>7,8</sup> This may also cause considerable problems in sports competitions and should be taken into account when planning journey times for sportsmen.<sup>8</sup>

A chronobiotic is a class of drug that can alter the circadian rhythms, and melatonin falls into this class. Melatonin is secreted in the body during the night and influences the body clock.<sup>8</sup> Much research has been carried out on the use of melatonin in sleep disorders and jet lag. A double blind trial was carried out in 1986, using 17 volunteers who flew from London to San Francisco. Having adapted to the new time, the volunteers were flown back to London. For three days before the return flight, a dose of 5mg melatonin or placebo was taken at 6pm local time and following the return to Britain the dose was continued for a further four days, between 10pm and midnight local time. None of the melatonin group suffered appreciable jet lag.<sup>9</sup> Although this study used a small sample of subjects, it showed the first promising results using melatonin for jet lag.

In a similar study,<sup>10</sup> 20 volunteers flew eastwards from Auckland, New Zealand, to London and returned after three weeks. Subjects took either placebo or 5mg melatonin for the first journey and vice versa for the second journey, in a double blind test. Less jet lag was experienced in the travellers taking melatonin than in the placebo group. The dose of 5mg melatonin was well tolerated with few side effects reported (a mild sedative effect in two subjects and a relaxed feeling in another). As in the former study the results were favourable, but the conclusion was that more research was necessary to determine the optimum dose and dosing

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schedule. In addition, the symptoms of jet lag were not standardised in either study and were subjective, making comparisons difficult. Moreover, factors such as previous fatigue, stress due to travel preparations and the flight itself, possible inability to sleep in a new environment and the extent of business or other activities, were not taken into account. It is, therefore, hard to say which effects were due to the jet lag and improved specifically by melatonin.<sup>7</sup>

These problems were addressed in a recent study.<sup>7</sup> The sample size was large (n=257) and a scale was used to assess the severity of the jet lag experienced, including daytime symptoms, when travelling from New York to Oslo. A randomised, double blind procedure was used in which subjects received either placebo or 5mg melatonin at bedtime, 0.5mg melatonin at bedtime or 0.5mg melatonin taken on a shifting schedule. The results were somewhat surprising in that melatonin did not show significant improvement over placebo.

However, the authors admitted that the study had various limitations. Day time disturbance, times of sleep onset at night and awakening in the morning were examined. But symptoms of sleep disturbance, which are associated with jet lag, were not investigated. In addition, the subjects remained only four days at their destination before flying back and might not have fully adjusted to the local time. There may also have been a large placebo effect, as the subjects knew that they had three out of four chances of receiving melatonin, and this would make the actual melatonin effect even smaller. The authors concluded that more work is needed to assess the use of melatonin in jet lag.

**Sleep disorders** Sleep disturbances are common, especially in the elderly. These can be primary, age-related disorders, or secondary to drugs (eg, beta-blockers can cause sleep disturbance), illness (pain, discomfort, etc), or anxiety and stress. Side effects of drugs (eg, increased urination, gastrointestinal effects, nausea) can also cause interference with sleep.<sup>4</sup> In melatonin studies, it is therefore important to try to eliminate secondary causes of sleep disorders when recruiting volunteers.

Six healthy young men were used in a study to investigate the effect of melatonin given at night.<sup>11</sup> None of the subjects suffered from any sleep disorders or took any medication, and they refrained from alcohol and caffeine for 24 hours before each session. It was found that doses of 0.3mg and 1mg melatonin given at 8pm or 9pm produced acute hypnotic effects. These effects were assessed both subjectively and using polysomnographs (using electroencephalographic electrodes). The authors suggested that a critical plasma melatonin level may be necessary for sleep induction. There was no residual hypnotic effect on the morning following melatonin administration, as shown from the results of mood and performance tests carried out by the volunteers. These results are promising for melatonin administration in insomniac patients.

## POSSIBLE USES FOR MELATONIN

Based on its physiological roles, melatonin has been investigated for many different uses.

- Since it controls the body's circadian rhythms, it has been widely researched as an aid to jet lag and problems related to insomnia
- It has been found to be a powerful free radical scavenger and as such its use as an antioxidant and in ageing has been studied.
- The role of melatonin in the immune system and in cancer has led to research in these areas.
- It has also been found to be involved in seasonal breeding of animals and its effects on human reproduction have been studied.

In a study involving 20 subjects who met the criteria for primary insomnia,<sup>12</sup> it was found that between 6pm and 11.30pm there were significantly lower concentrations of melatonin in the plasma of insomniacs than in the 20 controls matched for sex and age. This small study suggests that the lower plasma melatonin levels could have affected sleep in these subjects.

Melatonin has a half-life of only 40–50 minutes, with serum concentrations after oral dosing reaching peak levels after 20 minutes. So, to ensure high serum levels throughout the night, either a high dose or frequent low doses would have to be given. A controlled release tablet of 2mg melatonin was formulated to overcome these problems, and this was tested in elderly insomniacs who were on various medicines.<sup>4</sup> The patients, who were from a senior citizens' home, were taking between one and six drugs and also used sleep medication. Before starting the study, the subjects were woken every three hours during one night, to measure urinary 6-SMT. The authors compared the values obtained then to values from an earlier study, using elderly people without insomnia. In all subjects the peak excretion of 6-SMT occurred between 3am and 6am, rather than from midnight as occurs in young adults and elderly people without insomnia. This indicated that the sleep disorders might well be due to the decrease in plasma melatonin.

Actigraphy was then used to assess sleep patterns for three nights. This method uses wrist movements to assess sleep patterns while the subject is in his or her own bed. This makes it a good tool for long-term studies in the elderly. A random, crossover design was used, in which the subjects were given 2mg controlled release melatonin, or placebo, two hours before bedtime, for three weeks. Actigraphy was used again for three nights at the end of the study. Results showed an overall improvement in sleep quality in the test subjects despite chronic disease states and concomitant medication.

The authors commented on why their

study showed positive results, whereas other studies reported in the literature did not. First, as described above, it is necessary to establish melatonin deficiency in the subjects used. Secondly, the controlled release formulation might have prevented desensitisation to large doses required for the same plasma concentration. A minimum of three weeks' treatment is also important, as it has been shown in animal studies that melatonin receptors can be reduced in the elderly and need to be resensitised by long-term exposure. A further reason given is that the internal clock in the elderly is sometimes not synchronised with the light-dark cycle and exogenous melatonin will correct this over a few weeks.

An interesting case has been reported<sup>13</sup> of a young woman who suffered excessive drowsiness, which became more severe after childbirth. At the age of 13 she had undergone partial resection of what was thought to be a pinealoma. On admission to hospital, at age 24, the woman spent most of the day sleeping. Urinary melatonin levels were found to be low and unrelated to circadian rhythms. After eight weeks on 2mg melatonin at night, the patient showed usual sleep patterns, taking only a 20 minute nap during the day. It was interesting to note the increased severity of somnolence following pregnancy, which improved with melatonin therapy.

There is a rare genetic disorder called Angelman syndrome (AS), which is characterised by many symptoms, including mental retardation and hyperactivity. Disturbed sleep, which is difficult to treat using traditional sedatives, is also evident. This normally starts at a few months of age and may cause severe problems for the patient and carers. Melatonin was investigated in AS in a recent study.<sup>14</sup> Although normal children have high melatonin levels and should not require melatonin therapy, in unusual cases such as this, melatonin has been given to children. Low dose (0.3mg) melatonin was given to 13 children, half to one hour before their usual bedtime, for six nights. There was an improvement in sleep patterns and a reduction of motor activity during the sleep period. This was accompanied by moderate increases in melatonin levels. Of the 13 patients, 12 agreed to extend the study for a year.

**Ageing and antioxidant properties** In a remarkable experiment,<sup>15</sup> the pineal gland was removed from the skulls of young adult (3–4 months) and old (18 months) genetically pure, inbred mice, and transplanted from one group to the other. Control mice were operated on in the same way, but the original pineal gland was replaced. Physical conditions, body weight and life span were then compared in the mice. A significant increase in both ageing and death were seen in the mice transplanted with an "old" pineal gland while in the old mice transplanted with a "young" pineal, ageing and death were slowed. In both cases the difference in ageing was six months — a quarter of the life span for that strain of mice. This experiment clearly demonstrates the importance of the

pineal gland in ageing and death.

In a study measuring melatonin production in 60 healthy subjects, melatonin decreased with age and this may have significance for ageing in humans.<sup>16</sup>

Degenerative diseases increase with age. The increasing amount of evidence in both of these areas strongly indicates that there is a definite relationship between degenerative disease and decreased melatonin production. Oxidative stress as a result of free radical reactions is one theory helping to explain ageing and age-related disease. When endogenous antioxidants are depleted or when free radicals increase, both of which can occur due to toxins and in advancing age, oxidative damage occurs. This leads to degeneration of cells and organs, resulting in loss of function and disease. Endogenous antioxidants, and exogenous supplements, like vitamins C and E, are important to prevent oxidative damage.<sup>17</sup>

In 1993 it was discovered that melatonin acted as a hydroxyl radical scavenger.<sup>18</sup> Since melatonin had been reported to have anti-ageing properties and to protect against DNA damage, it was speculated that melatonin might exhibit antioxidant activity, since oxidation was common to both anti-ageing and DNA damage. In contrast to other antioxidants, such as ascorbate, which are either pro-oxidant or antioxidant depending on the physiological conditions, melatonin did not show any pro-oxidant effects. The experiments using melatonin were carried out *in vitro* and at concentrations far exceeding those found under normal conditions, but they did show that melatonin was a potent antioxidant, with high lipophilicity and no toxicity.

Since that time, much work has been published investigating the role of melatonin in scavenging many other reactive species, as well as its ability to stabilise lipid membranes, so enabling them to resist oxidative damage. This action of melatonin is independent of any receptor binding and this may be partly due to the stimulation of intracellular antioxidants, such as glutathione and inhibition of oxidising enzymes, such as nitric oxide synthase. Reiter provides a detailed review of melatonin and its antioxidant properties.<sup>19</sup>

However, the pharmacological doses used to achieve an antioxidant effect are far higher than the endogenous physiological concentrations present in the body. Furthermore, most studies to date have used animal models rather than humans,<sup>19,20</sup> and application of study results to humans must be made with caution. It is too early to promote the use of melatonin as an anti-ageing supplement and more work is required in this field.

**Cancer and enhanced immunity** Melatonin has shown both *in vitro* and *in vivo* inhibition of various types of cancer cells.<sup>2</sup> Evidence for the role of melatonin in cancer therapy is conflicting, but most studies show positive results and a low level of endogenous melatonin has been shown in cancer patients.<sup>20</sup>

A group of 80 patients with advanced

solid tumours, all of whom refused chemotherapy or did not respond to previous chemotherapy, were entered into a study.<sup>21</sup> The patients randomly received either interleukin 2 (IL-2) alone for four weeks, or IL-2 with melatonin (40mg, starting one week before IL-2). The addition of melatonin increased the anti-tumour activity of low-dose IL-2, resulting in accelerated tumour regression, increased progression-free survival and longer overall survival in these patients.

In another study involving 14 women with metastatic breast cancer,<sup>22</sup> melatonin was shown to increase the effects of tamoxifen. As in the previous study melatonin (20mg) was started seven days before the tamoxifen. This small investigation provides preliminary evidence that melatonin could have a role in cancer therapy, but large clinical trials are required to provide conclusive evidence.

In patients with solid neoplasms, brain metastases present a serious condition. Although chemotherapy and radiation therapy has been tried, there is no clear prolongation of survival time, and survival time is often less than six months in these patients. A study was performed on 50 such patients,<sup>23</sup> who were treated by supportive measures (steroids and anticonvulsants) alone or with the addition of 20mg melatonin daily. Survival at one year was significantly higher in the patients receiving melatonin. Other benefits of the melatonin treatment included a clear improvement in the quality of life and a reduced frequency of steroid complications, compared with the group receiving supportive care alone. This study justifies further work in this area, including large clinical trials to evaluate the use of melatonin in different types of cancer.

It is possible that melatonin exerts its anticancer properties through the immune system, and it has been shown that melatonin enhances immune responses.<sup>20,24</sup> This effect is even more pronounced in immunocompromised states, including those resulting from stress, corticosteroid therapy and viral disease. Melatonin also seems to protect the cells against damage from cytotoxic agents. However, melatonin has also been shown to act as an immunosuppressant,<sup>25</sup> worsening such conditions as auto-immune disease and severe allergies, so care is needed before treatment is considered.

**Reproduction** Most studies on reproduction and melatonin have been carried out in animals. However, many animals exhibit a seasonal reproduction cycle, which may be affected by melatonin levels. The role of melatonin in non-seasonal breeders, such as humans, has not been defined but should be considered when starting melatonin therapy.<sup>2</sup> It has been suggested that the onset of puberty is related to the decrease of melatonin which occurs as children grow, and children who have an early puberty have low levels of melatonin.<sup>3</sup> Few studies have been carried out on women, although in one interesting experiment involving young women, a large dose of 300mg daily for four months partially inhibited ovulation. This

effect was increased by the addition of a progestin minipill. Side effects with melatonin when used as a contraceptive included abnormal bleeding and headaches, but interestingly, no effect on sleep was reported.<sup>22,24</sup>

**Miscellaneous** Melatonin has been used in other situations, but many of these suggested uses are based on animal studies and there is insufficient evidence in humans. Examples include lowering cholesterol, coronary heart disease, epilepsy and cluster headaches.<sup>2</sup>

A novel use of melatonin has been described,<sup>26</sup> in which melatonin was used in the reversal of morphine dependence in mice.

## DRUG INTERACTIONS

It is not advisable for melatonin to be taken with tranquillisers or antidepressants.<sup>6</sup> Benzodiazepines are reported to decrease nighttime melatonin levels and increase daytime levels. This could explain the residual effect of benzodiazepines felt the following morning and could also be related to the rebound insomnia following withdrawal of treatment.<sup>11</sup>

Beta-blockers are known to cause sleep disturbances. In a study of 15 healthy males, propranolol and atenolol reduced nocturnal melatonin levels by specific inhibition of adrenergic beta<sub>1</sub> receptors.<sup>27</sup> In another study,<sup>28</sup> a significant reduction in melatonin levels was reported only after using metoprolol and not with atenolol or propranolol, although there was a tendency to lower melatonin levels with all three drugs. There may therefore be a place for the use of melatonin to avoid sleep disturbances in patients on beta-blockers, but further clinical trials are necessary.

Other commonly used drugs have also been found to cause a decrease in nocturnal melatonin secretion. Examples include fluoxetine<sup>29</sup> and the non-steroidal anti-inflammatory drugs indomethacin and ibuprofen.<sup>30</sup>

Melatonin preparations may be contaminated by tryptophan and related substances, and should therefore be avoided in patients taking monoamine oxidase inhibitors.

Two small studies found that oral ethanol, in amounts sufficient to produce mild intoxication, inhibited melatonin levels. This may be part of the reason why ethanol causes sleep disturbances, including an increased readiness to fall asleep but poorer sleep quality.<sup>31,32</sup> The disturbance in endogenous rhythms, after mild or moderate intoxication, may be the cause of altered mental alertness and increased fatigue on the morning following such behaviour.

## SIDE EFFECTS

Melatonin is generally considered to be safe. It has been argued that even in very high doses (300mg/day) melatonin is safer than many over-the-counter remedies presently on sale. With appropriate use melatonin has

a high safety record.<sup>5</sup> However, long-term data on safety are not yet available.

In America, elderly insomniacs use melatonin freely. This is a cause for concern because insomnia is often part of a depressive disorder, which melatonin could worsen.<sup>1</sup> With doses of 5mg, effects on mental performance have been reported, but if the subject is allowed to sleep after melatonin ingestion, no residual effects are noticed on waking.<sup>8</sup> In 10 years of jet lag studies, Arendt, a leading researcher of jet lag, has found that daytime sleepiness occurs in about 8 per cent of subjects given a 5mg dose.<sup>1</sup> In one study of 572 subjects, one traveller reported difficulties in breathing and swallowing within 20 minutes of taking 0.5mg melatonin, symptoms which lasted for 45 minutes. After the study, the subject took another dose and similar, but milder symptoms occurred.<sup>7</sup>

Reports on the side effects of melatonin used for insomnia are conflicting. Some studies suggest that melatonin is safe even in high doses,<sup>1</sup> whereas others claim that in 10 per cent of people using melatonin at high dose, insomnia and nightmares have occurred.<sup>25</sup> Although the dose required to induce sleep is between 0.1 and 0.3mg, doses of 2 to 3mg are available.

The effect of melatonin on driving performance has been studied with the overall result being that melatonin did not adversely affect driving ability. However, caution should be exercised when driving after taking melatonin, because of the increased sleepiness which can occur.<sup>33</sup>

In a study in the elderly, pruritis was noted in one out of 12 participants taking 2mg melatonin for three weeks.<sup>4</sup> In addition, an unusual side effect has been reported recently.<sup>34</sup> A man suffering from amyotrophic lateral sclerosis (ALS), a degenerative motor neurone disease, developed painful gynaecomastia. The patient had been taking melatonin 1mg/day increasing to 2mg/day in the previous 18 months, as well as riluzole, citalopram and vitamin E. On stopping the melatonin, symptoms resolved spontaneously. This

case demonstrates that the absence of side effects in healthy people does not necessarily mean that melatonin is safe for everyone.

In general, melatonin can be thought of as a beneficial and safe supplement, but caution must always be employed before starting therapy. The minimum dose should be used in each case and it should be avoided in the following groups of patients:

- Women wishing to conceive and those who are pregnant or breast feeding. (Maternal melatonin crosses the placenta and there are melatonin receptors in the foetus from an early stage of development. High placental melatonin concentrations can lead to foetal abnormalities.<sup>33</sup>)
- People with allergies or autoimmune disease
- Children
- Patients with severe mental illness
- Patients taking monoamine oxidase inhibitors

hibitors

## CONCLUSION

If the present interest in melatonin continues, the many questions as to its place as either a nutraceutical or indeed as a licensed medicine may begin to be answered.

Melatonin certainly seems to be an interesting substance, which, with cautious use has many benefits. However, until its safety and efficacy have been proven, users of this supplement, whether for jet lag, insomnia or as an antioxidant, should be advised to do so with caution.

## NUTRACEUTICALS

Publication of this article completes our series of eight articles on nutraceuticals. References for the complete set are given below:

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