



## Melatonin

### *Claims made in the popular media are mostly nonsense*

Melatonin, the hormone of the pineal gland, is currently the subject of much ill informed publicity and speculation in the entertainment media worldwide. Several books on the subject have made grossly exaggerated claims for its value, portraying it as a panacea and as an "anti-aging" treatment.<sup>1,2</sup> These claims are distortions of current knowledge of the physiological functions of melatonin and of its therapeutic potential.

What is known can be summarised briefly. Melatonin is normally made at night and may be considered to act as a signal of darkness to the body. In all life forms so far studied it seems to act as a time signal for the organisation of daily (circadian; sleep-wake) or seasonal rhythms, or both.<sup>3</sup> Melatonin seems to play an important part in setting the correct timing of sleep-wake cycles in mammals in the perinatal period and of subsequent pubertal development. When given to humans it has rapid, transient, mild, sleep inducing effects,<sup>4</sup> and it lowers alertness, body temperature and performance during the three or four hours after low doses have been given.<sup>5,6</sup> Correctly timed, it is able to shift the internal "body clock" both to later and earlier times,<sup>3,7</sup> and so melatonin has a potential value as a treatment for problems with sleep and other body functions that have been disordered by time effects.

The common ways in which time rhythms are upset include long distance air travel, shift work, and certain types of insomnia. Some blind people cannot maintain a 24 hour rhythm of sleep and waking.<sup>3,8</sup> Even normal healthy people may show a tendency for the internal clock to delay, telling them to sleep later than is socially and professionally desirable. Some

authors have described a "melatonin deficiency" syndrome related to poor sleep in old age, but whether this is specific or simply related to declining circadian function is debatable.<sup>9</sup> Serum concentrations of melatonin can (albeit rarely) be very low in young, healthy, adults.<sup>3</sup> The timing of treatment with melatonin can be predicted when body clock time is known, and to some extent this may be judged by the habitual time of going to sleep and the duration of sleep. Optimal timing is not so simple after travel across time zones and in shift workers—and mistiming the dose might be expected to lead to major problems of alertness. Nevertheless, there is substantial published evidence showing that a carefully timed dose of melatonin can improve both the subjective and objective symptoms of jet lag.<sup>10</sup> The only serious side effect reported has been sleepiness after the dose. An improvement in daytime sleep and night time alertness was shown in simulated night shift work and in two small field studies.<sup>10</sup> Much more research is required, especially on work related performance.

### **No objective measures of success**

Melatonin has also proved quite useful in disturbed sleep-wake cycles in visually impaired people, in the delayed sleep phase syndrome, in multiply disabled children,<sup>3</sup> and apparently in insomnia of the elderly.<sup>11</sup> It may improve the sleep quality of some normal healthy adults. For none of these conditions or indications have large trials been reported, and polysomnography has given inconsistent results, so that there

is no objective measure of success. Nor is melatonin free of drawbacks: if it is given to people in certain unusual environments (such as people who live continuously in dim light), sleep can become fragmented (unpublished data).

Melatonin has been reported to have some antioxidant and immunostimulant effects at high concentrations—but pro-oxidant and immunosuppressant effects have also been described.<sup>1,2,12-14</sup> Melatonin has been claimed to inhibit the growth of cancer cells in vitro, but it can promote melanoma growth in hamsters.<sup>15,16</sup> Clinical trials of its use as an adjunct to chemotherapy and immunotherapy are still at too early a stage for the results to be evaluated.

Melatonin has been investigated as a contraceptive, given at huge doses (75-300 mg daily) combined with a progestin minipill, and curiously no effects on sleep have been reported in these trials.<sup>17</sup> Side effects included abnormal bleeding and headache. It can affect human reproductive hormones in lower doses.

Claims that melatonin slows aging are apparently based on research using strains of mice with a genetic deficiency in the ability to make melatonin—making the results of dubious applicability to humans.<sup>18</sup> There is no scientific evidence at all that melatonin will extend the normal human lifespan, improve cardiovascular and sexual function, or cure Alzheimer's disease or AIDS, as claimed in some popular texts.

#### Safety remains uncertain

Questions of safety have yet to be resolved and so are of great importance. No doses have yet been agreed for any condition, although dose-response studies suggest that for clock related problems 5 mg is more efficient than lower doses.<sup>6</sup> Pharmacokinetic studies of melatonin have given variable results, probably because of a large hepatic first pass effect.<sup>3</sup> Virtually no data are available to compare the efficacy of various formulations in different conditions. Acute studies on rodents have found low toxicity,<sup>19</sup> but no data exist on long term studies in humans. The effects of melatonin on human puberty, in lactation, in pregnancy on mother and fetus, and in combination with other medication are unknown.

Melatonin is available in Britain only on prescription on a named patient basis. If the American health food industry were to use some of its profits for evaluations of safety and efficacy, that would be a service to the millions of Americans reportedly taking melatonin. In the meantime the development of different formulations, agonists, and antagonists is awaited with interest.

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