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REVIEW

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Melatonin in elderly patients with insomnia

A systematic review

Melatonin bei älteren Patienten mit Schlaflosigkeit – Eine systematische Übersicht

Summary *Background* Melatonin is a hormone and antioxidant produced by the pineal gland of which four neurobiological roles have been claimed in the aged population: anti-ageing agent; free-radical scavenger; regulator of circadian rhythm; endogeneous sleep-inducer. The "melatonin replacement" hypothesis states that 1) the well-evidenced age-related decline contributes to insomnia and that 2) replacement with physiological doses of melatonin improves sleep. The aim of this review was to determine the evidence for the efficacy of melatonin in elderly insomniacs. *Methods* MEDLINE's database from 1990–2000 was searched with "melatonin", "geriatrics" and "(frail)-elderly" as major subheadings. This resulted in 78 articles: only studies with empirical treatment data were reviewed (N = 12). *Results* Six reports (abstract, research letter, retrospective case study, 3 open label studies) showed a trend towards efficacy of melatonin: sleep quality improved and in patients with Alzheimer's disease sundowning was reduced.

In 6 double blind, randomised crossover trials, a total number of 95 patients (mean ages: 65–79 yrs) were treated. Melatonin doses ranged from 0.5 mg to 6 mg; most took a single dose 30–120 min before bedtime. In 3 studies a slow release form was used. Sleep quality was objectively measured by wrist actigraphy (n = 4) and polysomnography (n = 2), and additionally subjective sleep quality was assessed (n = 2). Sleep latency decreased significantly in 4 studies. In 3 studies other measures of sleep quality (sleep efficiency, total sleep time and wake time during sleep) improved. Subjective sleep quality did not improve. No early-morning sleepiness occurred. Comparison of the studies suggests that melatonin is most effective in elderly insomniacs who chronically use benzodiazepines and/or with documented low melatonin levels during sleep. *Conclusion* There is sufficient evidence that low doses of melatonin improve initial sleep quality in selected elderly insomniacs. However, larger randomized controlled trials, with less strict inclusion criteria are necessary to yield evidence of effectiveness (i.e. clinical and subjective relevance) in geriatric patients who suffer from insomnia, before wide-spread use can be advocated.

Key words Melatonin – insomnia – sleep – circadian rhythm

Zusammenfassung *Hintergrund* Melatonin ist ein Hormon und Antioxidans, das in der Epiphyse produziert wird. Vier neurobiologische Rollen werden dieser Substanz zugeschrieben: Antiageing-Mittel, freier Radikalenfänger, Regulator des zirkadianen Rhyth-

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mus sowie endogener Schlafanstoßer. Die Melatoninersatzhypothese geht davon aus, dass 1. der gut belegte altersabhängige Rückgang zur Schlaflosigkeit beiträgt und das 2. der Ersatz durch physiologische Dosen von Melatonin den Schlaf verbessert. Ziel dieser Übersichtsarbeit war die Evidenz für die Wirksamkeit von Melatonin in älteren schlafgestörten Menschen zu untersuchen. *Methoden* Die Medline-Datenbank von 1990 bis 2000 wurde mit den Begriffen „Melatonin", „Geriatrics" und „(Frail)-Elderly" abgefragt. Es fanden sich insgesamt 78 Artikel. Nur Studien mit empirischen Behandlungsdaten wurden gereviewt (n = 12). *Ergebnisse* Sechs Berichte (eine Zusammenfassung, ein Research letter, eine retrospektive Fallstudie, 3 Open label Studien) zeigten einen Trend im Hinblick auf die Wirksamkeit von Melatonin: Die Schlafqualität verbesserte sich und bei Patienten mit Alzheimerscher Erkrankung trat das sogenannte Sundowning-Syndrom vermindert auf.

In sechs doppelblinden randomisierten Crossover-Studien wurde eine Gesamtzahl von 95 Patienten (mittleres Alter 65–79 Jahre) behandelt. Die Melatonindosis reichte von 0,5 mg bis 6 mg. In den meisten Studien wurde eine Einmalgabe 30–120 min vor dem Schlafengehen verabreicht. In drei Studien wurde eine retardierte Form benutzt, die Schlafqualität wurde objektiv gemessen durch Handgelenksaktigraphie (n = 4) und Polysomnographie (n = 2). Zusätzlich wurde die subjektive Schlafqualität in zwei Studien bewertet. Die Schlaflatenz verminderte sich in vier Studien signifikant, in drei Studien verbesserten sich andere Messparameter der Schlafqualität wie Schlafeffizienz, Gesamtschlafzeit und Aufwachen während des Schlafes. Die subjektive Schlafqualität verbesserte sich nicht. Es trat keine morgendliche Schläfrigkeit auf. Der Vergleich der Studien legt die Vermutung nahe, dass Melatonin am besten bei älteren Schlafgestörten wirkt, die chronisch Benzodiazepine einnehmen und/oder niedrige Melatoninspiegel während des Schlafes aufweisen. *Schlussfolgerung* Es finden sich hinreichend Belege, dass niedrige Dosen von Melatonin die initiale Schlafqualität bei ausgewählten älteren Menschen mit Schlafstörungen verbessern. Es sind jedoch größere randomisierte kontrollierte Studien nötig mit weniger strengen Einschlusskriterien, um den Nachweis der Wirksamkeit (im Sinne einer klinischen und subjektiven Relevanz) bei geriatrischen Patienten zu erbringen, die an Schlaflosigkeit leiden. Erst dann kann eine breite Anwendung empfohlen werden.

Schlüsselwörter Melatonin – Insomnia – Schlaflosigkeit – Schlaf – zirkadianer Rhythmus

"Oh sleep! It is a gentle thing,
beloved from pole to pole."

T.S. Coleridge

Introduction

Melatonin is the principal hormone produced by the pineal gland, which Descartes described as the seat of the soul. Within the pineal gland, melatonin (N-acethyl-5-methoxytryptamine) is synthesised from serotonine (5-hydroxytryptamine) in a clear circadian rhythm. This results in a nocturnal production of melatonin, controlled by the circadian clock in the supraschiasmatic nucleus (SCN) in the hypothalamus, through β-adrenergic receptors in the pineal gland. In the last decade, a lot has been speculated about the physiological and the potential pharmacological roles of melatonin in the aged. Culmination of the speculations were publications with the headings "the melatonin miracle" and "melatonin madness" (Pierpaoli and Regelson, 1995). Gradually it became clear that melatonin has a role as secondary "Zeitgeber" in regulating circadian rhythm in man. Though less important than light in the regulatory effects, this hormone effect has been translated already in a well-evidenced pharmacological application of melatonin in disturbances of the circadian rhythm such as in jet lag and shift work (Herxheimer and Petrie, 2001).

In ageing, four possible roles of melatonin administration have become clear. It can act as an anti-ageing drug, an anti-oxidant drug, a restorer of disturbed circadian rhythm, and an anti-insomnia drug. Of course the first two and the latter two roles are interrelated. In vivo studies in mice resulted in contradictory results with regard to anti-ageing effects. At the moment, there is no solid empirical base for melatonin as an important anti-ageing drug (Yu, 1999). However, because the causality of ageing is very likely to be multifaceted, it would be very unlikely for a single intervention (e.g. melatonin supplementation) to be capable of preventing ageing. If there would be an effect, melatonin probably should exhibit its effects on ageing by immunoenhancing and anti-oxidant properties. Reiter recently reviewed the evidence on melatonin's anti-oxidant effects (Reiter, 2000). He concludes that though melatonin

is the only anti-oxidant drug known to decrease substantially after middle age, its role in reducing oxidative stress in ageing in uncertain, because of contradictory results in animal studies.

Several studies have been performed to describe the relationship between the changes in the melatonin rhythm in ageing and the occurrence of sleep disorders in the elderly. Despite large inter-individual differences within age groups, most studies show a marked difference in the features of the melatonin rhythm when young and elderly healthy subjects are compared (Ohashi et al., 1998; Sharma et al., 1989; Thomas and Miles, 1989). On average, the nocturnal peak of melatonin in the elderly is lower and the decline of the melatonin level from the nocturnal peak starts earlier. In elderly hospitalized patients and in patients with senile dementia of Alzheimer's type (SDAT) (Mishima et al., Ohashi et al., 1999) the diurnal melatonin secretion becomes further disrupted. In these patients, melatonin production also takes place during the daytime and the nocturnal peaks become more and more fragmented, resulting in a chaotic 24 hour pattern, still characterised by large inter-individual differences. When comparing elderly patients with and without sleep disturbances and elderly demented patients with and without a disturbed sleep-waking cycle, the group of patients with sleep disorders show a more pronounced fragmentation of the circadian melatonin variation (Mishima et al., 1999; Haimov et al., 1994). Based on the data acquired by these cross-sectional, descriptive studies Hughes et al. formulated the "melatonin replacement hypothesis". The two components of this hypothesis are 1) the age-related decline in melatonin in some way contributes to insomnia, and 2) replacement therapy with high physiological doses of melatonin will improve sleep (Hughes et al., 1998). In this systematic review, we will focus on the empirical evidence for the melatonin replacement hypothesis. However, before presenting the data of the randomised, controlled trials carried out in elderly subjects, it is necessary to shortly review the pharmacological data to be able to evaluate study designs and to judge whether "physiological replacement doses" of melatonin were administered appropriately.

Pharmacologic profile of melatonin

Melatonin is an endogeneous compound, which cannot be patented by drug companies. Therefore, the industry so far has not been interested in performing large clinical trials. At the moment, synthetic melatonin is available in several countries as a food additive or an alternative pharmacological agent. In younger subjects, doses of melatonin commonly prescribed (0.3–0.5 mg) result in blood levels much higher than physiological levels (Waldhauser et al., 1984). Melatonin is rapidly metabolised by the liver and more than 85% is excreted in the urine as 6-sulphatoxymelatonin (6-MT). The half-life of melatonin is 30–50 min in young adults, and this short half-life may be the reason why most studies did not find a "hangover" (Waldhauser et al., 1984). However, a single dose of melatonin given before going to sleep will not give the physiological profile of nocturnal melatonin release, which shows on average a peak concentration shortly after midnight in the elderly (at one or two o'clock at night) (Ohashi et al., 1998). Therefore, sustained-release forms of melatonin were developed. From an open label study in elderly subjects, which was carried out by Shah et al., it becomes clear that a sustained-release dose of 0.1 mg results in an increase in the serum melatonin concentration of 30–40 pg/mL, which may be adequate for elderly with sleep disorders. Probably, a higher dose, such as the 0.4 mg dose, which was also used by Shah et al., is needed to reach the nocturnal melatonin levels that are common in younger subjects. The sustained-release (sr) dosage regimen turned out to have a half-life of about two hours in these healthy elderly subjects (n = 12; 6 men, 6 women; mean age 67 yrs). This melatonin-sr was given at 21.00 hours, which resulted in a maximum serum concentration in the early morning hours, approximately 5 hours after dosing, similar to the endogeneous profile.

In an extensive review of the literature on melatonin up to 1998, Avery et al. did not find important side-effects, apart from drowsiness 4-5 hours after taking melatonin (Avery et al., 1998). No cardiac or pulmonary problems, nor any other side-effects were reported, though there are known interactions with other endogeneous sex hormones (e.g. LH, FSH). So far, this interaction has not been proven to be clinically relevant. The other interaction that is clinically relevant is the one between light and the endogeneous melatonin release. Exposure to excessive ambient light in the evening will suppress physiological melatonin production (Avery et al., 1998). Therefore, both in trials and in clinical practice it is very important to control lighting conditions, especially in patients suffering from insomnia.

Methods systematic review

The Cochrane database for clinical trials and MEDLINE's database from 1990–2000, which is the relevant period for this subject, was searched with

"melatonin", "geriatrics" and "(frail)-elderly" as major subheadings and thesaurus terms. The search was extended using the references of the articles that were collected by the database search ("snow-ball method"). Based on the abstracts, all articles presenting empirical data were collected. For the assesment of evidence concerning the melatonin replacement hypothesis, only randomised clinical trials and meta-analyses were included.

Results

This systematic search of literature resulted in 78 articles, of which 12 studies presented empirical data. Six reports (abstract, research letter, retrospective case study, 3 open label studies) did not fulfill the design criterion of a being a randomised, controlled trial or meta-analysis. These 6 showed a trend towards efficacy of melatonin: sleep quality improved and in patients with Alzheimer's disease sundowning was reduced (Shah et al., 1999; Brusco et al., 1998; Brusco et al., 1999; Singer et al., 1997; Tozawa et al., 1998; Wurtman and Zhdanova, 1995).

In total, the search resulted in six small randomised, controlled studies, which all used a cross-over design (Hughes et al., 1998; Grafinkel et al., 1995; Haimov et al., 1995; Garfinkel et al., 1997; Dawson et al., 1998; Jean-Louis et al., 1998). In Table 1, the key characteristics of the studies are presented. Subsequently we will present the most important data from these studies concerning subject recruitment, the correlation between low melatonin and sleep quality (first part of the melatonin replacement hypothesis), the clinical efficacy (second part of the melatonin replacement hypothesis), and side effects.

Recruitment and selection

Altogether, 95 elderly patients with insomnia were treated in the selected trials, equally distributed among men and women. The recruitment of patients in all trials resulted in a highly selected patient group. Garfinkel et al. recruited their chronic insomniacs from their audience at lectures on sleep disorders. These subjects probably reflect the general population of elderly subjects the best, because apart from the sleep problems they suffered from a variety of chronic diseases (ischemic heart disease, spondylarthrosis, Parkinson's disease, diabetes, hypertension). In the second study of Garfinkel et al. inclusion was carried out similarly, but subjects additionally had to be chronic benzodiazepine users. Haimov

Table 1 Summary of the key results of 6 randomised, controlled trials of melatonin and sleep in elderly patients

Study (first author, year)		N	Age (mean ± sd)	Dose (mg)	Time (h before bedtime)	Duration treatment	Measurements	Sleep latency	Sleep efficiency	Wake time during sleep	Other findings
Garfinkel	1995	12	76±8	2 slow release (sr)	2 h	3 weeks	Actigraphy	–	↑	↓	Selected long-term insomniacs
Haimov	1995	26	73±4	2	2 h	1 week	Actigraphy	↓	–	NA	Subjects: melatonin deficient; differential design
				2 sr		1 week		–	↑	NA	
				1 (open end)		2 months		↓	↑	NA	
Garfinkel	1997	21	79±5	2 sr	2 h	3 weeks	Actigraphy	↓	↑	↓	Insomniacs, all benzodiazepine users
Dawson	1998	12	65±4	0.5 transbuccal	2 h	4 days	Polysomnography	–	–	–	Melatonin resulted in decrease in core temperature
Hughes	1998	14	70±7	0.5	30 min	2 weeks	Polysomnography	↓	–	–	Highly selected group (2% included)
				0.5 sr	30 min			↓	–	–	
				0.5	4 h after sleep			↓	–	–	No effect on subjective sleep; No correlation between melatonin levels and sleep quality
Jean-Louis	1998	10	68±16	6	2 h	10 days	Actigraphy	↓	–	–	2 demented patients; 8 pts mild cognitive impairment Melatonin improved cognition and mood

NA: Not applicable, i.e. not measured in study; Polysomnography consisting of EEG, EOG, EMG; –: no change; ↓/↑: statistically significant decrease or increase

et al. (1995) selected both independently living and institutionalised insomniacs, who were assessed as "melatonin deficient". In contrast to Garfinkel, Haimov et al. excluded all patients with so-called primary sleep disorders (e.g. sleep apnea syndrome, restless legs, parasomnia etc.) and other diseases. Of all studies, Hughes et al. used the most strict inclusion criteria, which were based on medical history (excluding co-morbidity) and polysomnographia (excluding primary sleep disorders and including only subjects fulfilling certain sleep disorder criteria). As a result, they could include only 14 patients (2%) out of the 700 telephone respondents they started with. The other two studies (Dawson et al. and Jean-Louis et al.) also applied extensive inclusion criteria (e.g. polysomnographia by Dawson), but exact attrition data from recruitment to inclusion stage are not presented. From their inclusion criteria, it becomes clear that they only included relatively fit elderly subjects with insomnia. In the case of the study of Jean-Louis, subjects were physically fit but suffering from mild cognitive impairment or dementia.

Correlation between low melatonin and sleep quality

In all patients studied by Garfinkel et al., insomniac patients had lower melatonin levels in serum than younger controls (control data from other study by Haimov et al.) as measured by the urinary excretion of 6-MT. Moreover, the peak concentration in insomniac patients was delayed compared to elderly without insomnia. The patients included by Haimov et al., were all melatonin deficient; however, from the paper it is not clear whether they were selected because of low levels of melatonin, or whether they turned out to have low melatonin levels (such as the case in Garfinkel's study). Dawson et al. and Jean-Louis et al. did not compare the melatonin levels and sleep quality with younger subjects, nor with elderly people who had no sleep complaints.

Hughes et al. report a thorough study on the correlation between melatonin levels in their circadian rhythm and sleep quality before and after melatonin replacement. First of all, it became clear that several subjects with sleep problems had peak plasma levels completely comparable to younger subjects. Moreover, measures such as maximum peak level and the area under the curve of melatonin production did not correlate with sleep quality measures.

A conclusion that can be drawn concerning the study on the relationship between melatonin release and sleep quality is that there does not seem to be a simple causal relationship between low melatonin levels and insomnia in elderly patients. Low nocturnal melatonin concentration may contribute to insomnia, but these probably are not the most important factors.

Melatonin's efficacy in elderly insomniacs

Melatonin's efficacy was measured in these trials by means of objective and subjective measures of sleep quality.

The most important objective measures used in all six studies are:

- Sleep onset latency (SL): the time elapsed between the subject's self-selected sleep time and sleep onset.
- Wake after sleep onset (WASO): summation of all the time spent awake during the sleep period.
- Sleep efficiency (SE): the percentage of time that the subject was in bed following sleep onset that was spent asleep.
- Total sleep time (TST): the amount of sleep that occurs between the time of sleep onset and sleep termination.

Subjective sleep quality was measured only by Jean-Louis et al. and Hughes et al., and was performed by visual analogue scales and a sleep diary, respectively. In none of the studies were clinically relevant changes in objective or subjective sleep measures defined beforehand.

In all but one (i.e. Dawson et al.) of the six studies, were some positive effects on objective sleep quality measured. Sleep latency improved most often and decreased in four studies. Melatonin did not improve any of the subjective sleep measures. The studies carried out by Garfinkel et al. showed the clearest positive results. In their first study, sleep quality, as measured by wrist actigraphy, improved in sleep efficiency (which was greater with melatonin (83%) than with placebo (75%)), and in WASO (decreased from 82 min to 49 min) after three weeks of melatonin replacement. Garfinkel et al. obtained results that were even more impressive in a similar group of patients who used benzodiazepines chronically: sleep efficiency increased even more, while sleep latency and the time awake after sleep onset decreased.

The study by Haimov et al. had a complex, differential design. Subsequently, placebo, 2 mg fast-release and 2 mg sustained-release melatonin were administered, all during 1 week. The 2 mg sustained-release melatonin showed significantly greater sleep efficiency and less activity during sleep than placebo. The 2 mg fast-release melatonin resulted in significantly shorter sleep latency (32 min) compared to placebo (54 min). In a 2-month open label extension

of this study, 1 mg of sustained-release melatonin was given to part of the subjects (n = 17), which resulted in a shorter sleep latency, improved sleep efficiency and less wake time during sleep compared to the placebo week at the start of the study.

The study by Hughes et al. was very carefully designed to overcome some of the limitations the authors had recognised in earlier studies. They found a significant decrease in sleep latency in all forms of drug administration (early, late and continuous type). However, the researchers may have disturbed sleep quality themselves by giving a second drug dose at midnight, for which they also had to wake the subject, and by also performing measurements at that time.

Jean-Louis et al. measured a decrease in sleep latency from 26 min to 15 min, by giving supra-physiological doses of 6 mg. In this group of mildly and moderately, cognitively impaired subjects, an improvement in mood and recall was also measured, but other neuropsychological tasks did not change.

Adverse reactions

In none of the studies there were more adverse effects reported for melatonin than for placebo. Only Garfinkel et al. actually reported adverse effects, though no serious effects were seen (prurigo in 1 patient on melatonin and in 1 patient on placebo).

Discussion

Overall, this systematic review of the literature on the pharmacological effects of melatonin on sleeplessness in elderly subjects suggests that melatonin might be helpful for some patients suffering from insomnia, especially for patients with initial insomnia. There are no side effects reported in these trials, nor are side effects known from extensive use in the United States for other indications (e.g. jet lag). The studies reviewed do not present data that suggest subjective improvement of sleep quality, nor increase of deep sleep stages (stage 3–4 sleep). The way in which melatonin improved sleep is still uncertain, and today there are only limited data that support the hypothesis that replacement of the physiological decline and phase-shift with ageing does improve sleep by itself. Other causal factors might be the hypothermic effect of melatonin, which decreases core temperature at night by 0.3–0.4 °C (± 40% of the circadian temperature amplitude). This hypothermic effect was also evidenced in two studies reviewed here (Hughes et al., 1998; Dawson et al., 1998). It has been suggested that the attenuated decrease in core temperature, caused by the decrease in melatonin release with ageing, in fact is the reason for the increasing prevalence of sleep problems in the elderly (Dawson et al., 1998). The reset of the circadian rhythm by melatonin is another possible explanation of the beneficial effects of melatonin on sleep. However, this mechanism is not supported further by the data from randomised, controlled trials.

The trials reviewed here have important limitations that jeopardise generalisation of the results to geriatric patients. The subjects of these studies were a very strictly selected group of relatively fit elderly people, who cannot be compared easily with frail geriatric patients. Whenever application in geriatric patients is considered, chances for a successful intervention are highest in patients who already use benzodiazepines. These drugs may augment the effect of melatonin on their receptors or they might be directly related to the decline in melatonin level by a benzodiazepine-mediated inhibition of melatonin release (Garfinkel et al., 1997). It would be worthwhile to conduct trials investigating whether melatonin could play a role in reducing the large and detrimental amount of benzodiazepines used by elderly patients.

Other limitations of (some of) the studies reviewed concern the technical measurements (actigraphy may not be completely reliable for patients lying silently in bed without being asleep), the lack of control of lightning conditions and the small number of patients included. Lack of power may be the reason why in most of the studies positive trends were seen for sleep efficiency and time awake after sleep onset, which did not meet criteria for statistical significance.

Conclusion

Having sleep problems in the elderly probably may be called a geriatric syndrome, because of their high prevalence, the multifactorial eatiology and the multifactorial interventions that are most likely to be effective. From the data presented, it becomes unlikely that just a decrease in serum melatonin levels explain the increase in sleep problems in the elderly. Other factors that are important are core temperature, number and length of daytime naps, light exposure and secondary "Zeitgebers" (meals, ritual activities etc.). When circadian rhythm is ready for sleep at night, the increasing daily need for sleep should initiate and maintain sleep. Co-morbidity, of course, may interfere with sleep by dyspneu, pain, urinary urge etc.

At the moment, the best evidence for effective and enduring relief of chronic late-life insomnia is presented by Marin et al., who performed a multifacet intervention in which a behavioural, a cognitive and an educational component were jointly applied (Marin et al., 1999). Attention for factors that may enforce the normal circadian rhythm in the sleep-wake cycle may contribute to such a multifactorial intervention. Factors that may help in regulating circadian rhythm are proper lightning, adequate serum melatonin levels, and core and environmental temperature during the night. Medication that may suppress melatonin release (β-blockers, calcium channel blockers, NSAIDs, fluoxetine, benzodiazepines, caffeine) should be reconsidered. During the day, there should be enough light (> 2000 lux), and in the evening there should be dim light conditions (< 200 lux) to improve sleeping, partly by enabling the individual's optimal melatonin rhythm.

At present, there is insufficient evidence to warrant regular prescription of melatonin in elderly insomniacs, especially in the case of co-morbidity. More research should be carried out in less selected populations of elderly insomniacs. There especially is a need for large clinical trials in which a combination of circadian rhythm regulators is tested. In a more scientific sense, further research is needed for clarification of the (changing) role of melatonin in sleep in elderly subjects.

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