American Journal of Advances in Medical Science
www.arnaca.com
eISSN: 2347 -2766

Original Research Article

Use of Ramelton in mild to moderate cases of Alzheimer's dementia: An open label preliminary study

Mona Srivastava [*1], Gyan Prakash Singh[2]

[*1] Department of Psychiatry, Institute of Medical Sciences ,Banaras Hindu University ,Varanasi Uttar Pradesh- 221005,India
[2] Division of Biostatistics, Department of Community medicine, Institute of Medical Sciences ,Banaras Hindu University ,Varanasi-221005, Uttar Pradesh, India

Abstract

Alzheimer's disease (AD), is a major age-associated neurodegenerative disease, characterized by a progressive loss of cognitive functions and ultimately results in premature death. It is hypothesized that the decreased levels of melatonin. Ramelteon was the first of series of compound molecules approved by the U.S. Food and Drug Administration. **The aim of the present work is to** assess the efficacy of Ramelton on the cognitive status of the patients suffering with dementia. All subjects were assessed at baseline then they were prescribed Ramelton 4mg for 2 weeks and gradually the dose was increased to 8 mg which was continued at 6 weeks and 12 weeks. It was observed that most of the subjects could tolerate 8 mg of Ramelton. A Wilcoxan analysis of the ADAS-cog revealed a significant change at 1st, 2nd, and 3rd follow up. In the present study, the improvement in sleep pattern was noted but the level was not statistically significant. Results from the present indicate that Ramelton needs a robust investigation as an alternative option in subjects having AD.

Key words: Alzheimer's dementia(AD);ramelteon; cognitive function; melatonin

Cite this article as :
Mona Srivastava, Gyan prakash Singh. Use of Ramelton in mild to moderate cases of Alzheimer's dementia: An open label preliminary study. American Journal of Advances in Medical Science. 2014; 2(2): 24-33.

Source of Support: Nil, **Conflict of Interest:** None declared.

1.0 Introduction

Alzheimer's disease (AD), is a major age-associated neurodegenerative disease, it is characterized by a progressive loss of cognitive function, loss of memory, impaired synaptic function, and a massive brain cell loss that ultimately results in premature death. Although the exact cause of the disease is under intense investigation, the prevailing hypothesis proposes that the depositions of amyloid β-protein- (Aβ-) containing senile plaques and intracellular neurofibrillary tangles are the major etiological factors in AD [1]. In addition to cognitive and memory dysfunction, sleep-wake and other circadian rhythm dysregulation, are commonly seen in AD [2-5]. These circadian rhythm disturbances are associated with disturbed melatonin rhythmicity and decreased circulating brain melatonin levels [6-8]. It is hypothesized that the decreased levels of melatonin, in fact, could contribute to the pathophysiology of AD in view than melatonin combines chronobiotic effect along with an effective antioxidant, anti-inflammatory, and antifibrillogenic properties (Figure-1) [9]. With this background, the replacement of brain melatonin levels has been suggested as a way of arresting the progress of AD and for correcting the circadian and sleep-wake disturbances associated with the disease. As melatonin is a short-lived molecule having a limited duration of action (half life = 0.54–0.67 hours) [10]), analogs with a high affinity for melatonin receptors and a longer duration of action have been synthesized with a potential therapeutic efficacy to treat insomnia and psychiatric disorders like depression and bipolar affective disorder [11]. Ramelteon was the first of these molecules approved by the U.S. Food and Drug Administration to be used in the treatment of insomnia [12] and its potential use in AD together with that of melatonin is discussed in many papers. CSF melatonin values are nearly 30 times higher than those in the blood; thus, the brain tissue has a higher melatonin concentration than any other tissue in the body [13]. Melatonin participates in many of its functions by acting through G-protein membrane receptors, the MT_1 and MT_2 melatonin receptors [14-16].It is noted that the CSF melatonin levels decreased even in preclinical stages (Braak stages-1) of AD even when patients did not manifest cognitive impairment [17] suggesting thereby that reduction in CSF melatonin may be an early marker (and cause) for incoming AD. In an initial study on 14 AD patients with 6–9 mg of melatonin given for 2-3 year period it was noted that melatonin improved sleep quality [18]. Sundowning, diagnosed clinically, was no longer detectable in 12 out of 14 patients. Reduction in cognitive impairment and amnesia was also noted.A melatonin agonist with higher affinity to melatonin MT_1 and MT_2 receptors and a longer duration would theoretically be beneficial in tackling sleep-wake and circadian rhythm disturbances. In this aspect, ramelteon, which is the first melatonin receptor agonist approved by FDA with activity on MT_1 and MT_2 receptors, should be

considered [19,20]. The selectivity of ramelteon for MT_1 has been found to be1000-fold over that of MT_2 receptors. It is well known that melatonin exerts its hypnotic effects through the activation of the MT_1 and MT_2 melatonin receptors [21]. On oral administration, ramelteon is rapidly absorbed with a T_{max} of less than 1 hour [22]. The absolute bioavailability of the oral formulation of ramelteon is less than 2% (range 0.5% to 12%) [22]. It is metabolized mainly in the liver via oxidation to hydroxyl and carbonyl groups and then conjugated with glucuronide. The adverse effects included mild gastrointestinal disturbances and nervous system effects such as dizziness, headache, somnolence, depression, fatigue, myalgia, and exacerbated eye pain [22].The encouraging reports about ramelteon, and a dearth of literature on the trial of this medication have prompted the present study

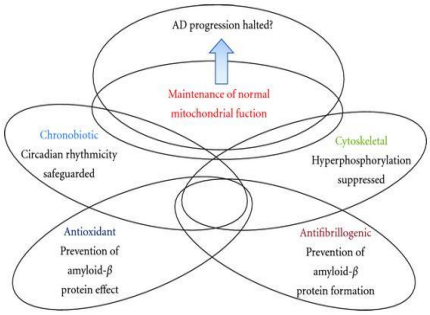

Figure-1: Effect of melatonin in halting AD (Source 9)

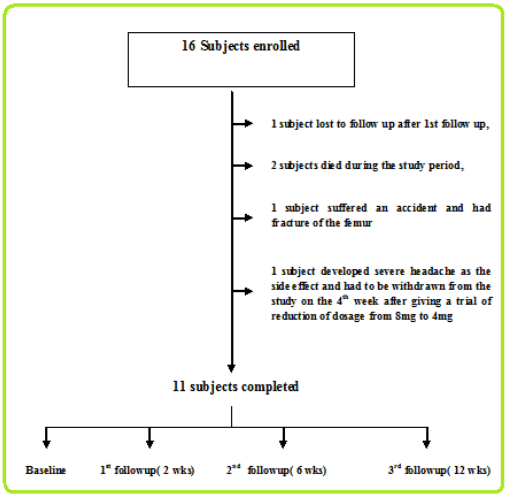

Figure-2: Flow chart of the study

2.0 Materials and methods

The study was a prospective study which was started in November 2012 and the intake of patients was continued till February 2014.All the patients presenting to the outpatient psychiatry section of Sir Sunderlal Hospital of the Institute of Medical Sciences, Banaras Hindu University were examined, if they complained of memory disturbance. The subjects were examined as per the diagnostic criteria laid down in DSM- IV [23], those subjects fitting the guidelines and fulfilling the criteria of Alzheimer's Disease were enrolled in the study. After enrollment the subjects were investigated for routine blood and biochemical parameters as per the dementia protocol to rule out any concomitant reversible cause of dementia. The subjects were examined by a MRI scan. All subjects meeting the criteria for probable Alzheimer's Dementia as laid down by NINCDS/ADRDA [24] were included in the study ,after fulfilling the inclusion and exclusion criteria.

The subjects were included if they had complaints of memory disturbance, met the criteria of probable AD (Alzheimer's Disease) as per NINCDS/ADRDA [24].

Table-1 : Socio-demographic profile of the subjects

Subject Number	Age in years	Sex	Duration of illness	Educational status & occupational status	Presenting symptoms
1.	66	F	12 months	Retired nursing superintendent, Graduate	Forgetfulness, reduced sleep, wandering away, restlessness during the evenings
2.	73	F	18 months	Retired school teacher, post graduation	Inability to recognize people, sleep disturbance, forgetfulness
3.	77	M	9 months	Retired police inspector, graduate	Forgetfulness, easy irritability, occasional urinary incontinence
4	62	F	12 months	Homemaker, graduate	Sleep disturbance, forgetfulness, stubborn behavior
5.	75	M	20 months	Farmer, matriculation	Forgetfulness, poor hygiene, sleep disturbance, wandering away
6.	70	M	9 months	Retired engineer, postgraduation	Forgetfulness, inappropriate smiling, sleep disturbance
7.	83	F	18 months	Homemaker, graduate	Forgetfulness, withdrawn, sleep disturbance
8.	64	F	10 months	Retired doctor, graduate	Forgetfulness, fecal incontinence
9.	70	F	12 months	Buissnesswoman, graduation	Sleep disturbance, gorgetfulness
10.	74	F	24 months	Homemaker, politician(gram pradhan), high school	Forgetfulness, sleep disturbance, talking more than usual
11.	68	F	10 months	Retired primary school teacher, graduate	Forgetfulness, hoarding behavior, sleep disturbance, wandering tendency

They were accompanied by a care giver, were literate, Mini Mental Status Examination(MMSE)[25] was a screening tool, those who scored between 24 to 14 on the scale(this parameter was arbitrarily decided to include only mild to moderate cases),a written informed consent was given by the caregiver. Exclusion criteria were those residing very far away so that early follow up was not possible, any concomitant physical, neurological or psychiatric problem, any substance abuse, including chewable tobacco like gutka, khaini. The study was approved by the ethical committee of the institute.

Table-2: Scores on cognitive scales and sleep quality

Subjects	MMSE score	ADAS-cog scores				Sleep Quality	
		Baseline	1st Assess.	2nd Assess.	3rd Assess.	Baseline	3 mnths.
1	22	20	20	19	17	poor	good
2	20	25	24	22	21	poor	good
3	18	30	30	28	26	fair	good
4	21	20	20	18	17	fair	Very good
5	20	18	17	17	17	fair	good
6	20	22	20	20	18	poor	Very good
7	22	25	24	22	19	poor	good
8	24	20	20	19	17	poor	fair
9	16	35	30	30	26	fair	Very good
10	18	26	24	22	22	poor	good
11	22	20	18	18	17	fair	fair

After intake the subjects were examined on the ADAS-cog (Alzheimer's Disease Assessment Scale-Cognitive subscale)[26].The care givers were explained about the study protocol and the subjects were started on 4mg of Ramelton(Ramitex^{R} Ranbaxy Limited ,India) the medication was given an hour before the usual sleep time of the subject.

Table-3: Wilcoxon Signed Ranks Test

Comparison	Mean	Sum	p value
Base - 1st follow up	4.00	28.00	0.001
Base - 2nd follow up	6.00	66.00	0.001
Base – 3rd follow up	6.00	66.00	0.001

Z = -2.401a

Asymp. Sig. (2-tailed) = .016

Following administration a brief explanation on the emergent side effects was given and an exhaustive psychoeducation session was given, as an add

on caregivers of the subjects were given an educative pamphlet on 'Dementia:A care giver's guide'(printed by the author's department for distribution to family members free of cost).As a precaution the care givers were given a prescription for haloperidol ,but were asked to use it as a last resort. The follow ups were fixed at 2week (1st follow up), 6weeks (2nd follow up), 12weeks (3rd follow up).The study period was fixed for three months, there after the subjects were given an option to continue or not. At first follow up the Ramelton was increased to 8mg, depending on the tolerability. The care givers were also asked to keep a sleep diary of the individual.
On all the follow ups the subjects were assessed on the ADAS-cog, any troublesome side effects were noted, general well being was assessed,a trouble shooting session and a reappraisal of the psychoeducation was done.

Figure-3: Improvement in sleep quality

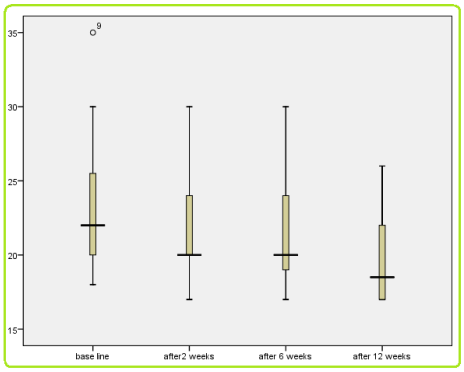

Figure-4: Comparison of ADAS scores at follow up

Tools

Socio demographic data sheet

A semi structured data collection proforma was used to collect the information regarding the sample population.

Mini Mental Status Examination

(MMSE by Folstein et.al.)[25] is a cognitive assessment tool which takes about 5 to 10 minutes to administer and is easy to score, we used the Hindi version which is well validated. Scoring is done from 0 to 30, with higher score meaning better functioning. The scores are divided into mild, moderate and severe, we included only mild and higher moderate scorers

Alzheimer's Disease Assessment Scale

(ADAS, by Rosen & Mosh, 1984)[26] is a commonly used scale to assess the cognitive and non cognitive deficits. This scale has two sub sections, we used the cognitive subscale i.e. ADAS-cog. It was designed to assess both cognitive and non-cognitive AD-specific symptoms [26]. The cognitive subscale, ADAS-Cog, is a standard tool in pivotal clinical trials to detect therapeutic efficacy in cognition. It consists of 11 subtests related to memory, praxis, and language which is measured by word recall, mazes, figure drawing, number cancellation tests etc. The scoring is done from 0 to 70, with a higher score indicating a poorer functioning. Depending on the AD stage of a patient, the

administration of ADAS-Cog takes 30 to 45 minutes.

Sleep diary

A rough estimate of the hours spent sleeping and number of awakenings, was monitored by the care givers.

3.0 Results and discussion

This was a prospective follow up study lasting for three months. We enrolled 16 subjects who fulfilled the criteria. The flow of study was thus(Figure-2) The average age of our sample was71years.There were 8(72%) females in our study, about 82% of our sample had done graduation .The average duration of illness of our sample was 14 months. The subjects belonged mostly to the Hindu community, with one subject being Christian and one being Muslim. The commonest presenting complaint was sleep disturbance and forgetfulness (Table-1). All the subjects except subject number7 could tolerate 8mg of ramelton, in the previous subject ramelton was decreased to 4mg and maintained on that dose. Table-2 shows the MMSE and the ADAS-cog scores of all the subjects. The average MMSE scores was20.2. The ADAS –cog scores were compared using the Wilcoxan paired test comparing the change in scores from baseline to 1st ,2nd and 3rd follow ups, the significance was fixed at 0.05level.The difference between the assessments was statistically significant($p<0.05$)(Table-3, Figure-4). The improvement in cognitive functioning was also related to improvement in sleep although the correlation was not statistically significant. The sleep quality showed improvement in almost all the subjects. Figure-3 shows that the sleep had improved in all the subjects from fair to very good when compared from base line to the last follow-up.

Our study included subjects belonging to either sex, having an average duration of illness of 14 months. Most of our subjects were females which is in keeping with the literature [24]. The average age of our sample was 71years, this finding is in keeping with the usual findings of the other studies [17]. Almost all our subjects were educationally qualified, this factor though is considered a protective factor but it can also imply that the cognitive decline is glaring when compared to the subject's original state [2]. The MMSE scores show that the subjects in the sample had milder form of dementia, on follow up a significant difference towards improvement was noted, this finding is in keeping with the finding in the other study [17], there are also findings to the contrary to what has been shown[18];however the study sample and design of the above studies could attribute to the difference in the findings. Sleep was much improved as per the anecdotal account, this is obvious as the primary function of ramelton is circadian rhytm regulation [21,22]. The subjects also reported to an improvement in the general well being as well. The feeling of wellness can partly be attributed to a improvement in sleep quality as has been found in the present study and other studies[9,11]

The study shows the advantage of the medication on the subjects, with the figure reaching the level of

significance. The study is a preliminary investigation which shows some promise for the use of ramelton as an alternative agent in mild to moderate cases of dementia this observation echoes the one reported in literature [12,20,22].Since there are very few reports regarding this particular compound this study could serve as a preliminary trial of an alternative agent. As a strength of the strength of the study , the assessment procedures used in the study are well validated and standardized, further significant improvement is noted in the scores. Commenting upon the limitations of the study, we would like to add that the study sample is too small to make a substantial conclusion, the study is an open label study which uses a short follow up time frame .We could not do an objective assessment of sleep and behavior ,the assessment was mostly anecdotal. Majority of the subjects belonged to mild dementia category, so effect on severe cases cannot be commented upon. As a future strategy large double blind multi centered trials may be undertaken to establish the efficacy of ramelton medication.

4.0 Conclusion

We would like to conclude that Ramelton as a medication deserves investigation as an alternative option in cases of dementia.The improvement in sleep is substantial and could translate into an improvement in the cognitive function of dementia patients.

Acknowledgements

All the subjects and their care givers.

.

Reference

1. Palop JJ, Mucke L. Amyloid-β-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nature Neurosci. 2010;13(7):812–818
2. Fotuhi M, Hachinski V, Whitehouse PJ. Changing perspectives regarding late-life dementia. Nature Rev Neurol. 2009; 5(12): 649–658
3. Beaulieu-Bonneau S, Hudon C. Sleep disturbances in older adults with mild cognitive impairment. Int Psychoger. 2009;21(4):654–666
4. Cochen V, Arbus C, Soto ME et al. Sleep disorders and their impacts on healthy, dependent, and frail older adults. J Nut Heal Aging. 2009;13(4):322–329
5. Vecchierini MF. Sleep disturbances in Alzheimer's disease and other dementias. Psychol NeuroPsychia Vieilliss. 2010;8(1):15–23
6. Skene DJ, Vivient-Roels B, Sparks DL et al. Daily variation in the concentration of melatonin and 5-methoxytryptophol in the human pineal gland: effect of age and Alzheimer's disease. Brain Res. 1990;528(1):170–174
7. Liu RY, Zhou JN, Van Heerikhuize J, Hofman MA, Swaab DF. Decreased melatonin levels in postmortem cerebrospinal fluid in

relation to aging, Alzheimer's disease, and apolipoprotein E-ε4/4 genotype. J Clin Endocrinol Metabol. 1999;84(1):323–327

8. K. Mishima, Tozawa T, Satoh K, Matsumoto Y, Hishikawa Y, Okawa M. Melatonin secretion rhythm disorders in patients with senile dementia of Alzheimer's type with disturbed sleep-waking, Biological Psychiatry. 1999;45(4):417–421.
9. Srinivasan V, Pandi-Perumal SR, Cardinali DP, Poeggeler B, Hardeland R. Melatonin in Alzheimer's disease and other neurodegenerative disorders. Behav Brain Fun. 2006; 2:15-19.
10. Aldhous M, Franey C, Wright W, Arendt J. Plasma concentrations of melatonin in man following oral absorption of different preparations. Brit J Clin Pharmacol. 1985;19(4):517–521.
11. Ferguson SA, Rajaratnam SMW, Dawson D. Melatonin agonists and insomnia. Expert Rev Neurother. 2010;10(2):305–318.
12. Pandi-Perumal SR, Srinivasan V, Spence DW. Ramelteon: a review of its therapeutic potential in sleep disorders. Adv Ther. 2009; 26(6):613–626.
13. R. J. Reiter and D. X. Tan, "Role of CSF in the transport of melatonin," Journal of Pineal Research 2002;33(1): article 61.
14. Reppert SM, Weaver DR, Ebisawa T. Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses. Neuron. 1994; 13(5):1177–1185.
15. Reppert SM, Godson C, Mahle CD, Weaver DR, Slaugenhaupt SA, Gusella JF. Molecular characterization of a second melatonin receptor expressed in human retina and brain: the Mel(1b) melatonin receptor. Proceedings of the National Academy of Sciences of the United States of America. 1995;92(19):8734–8738.
16. Dubocovich ML, Delagrange P, Krause DN, Sugden D, Cardinali DP, Olcese J. International union of basic and clinical pharmacology. LXXV-Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. Pharmacol Rev. 2010;62(3):343–380.
17. Zhou JN, Liu RY, Kamphorst W, Hofman MA, Swaab DF. Early neuropathological Alzheimer's changes in aged individuals are accompanied by decreased cerebrospinal fluid melatonin levels. J Pin Res. 2003; 35(2):125–130.
18. Brusco LI, Marquez M, Cardinali DP. Melatonin treatment stabilizes chronobiologic and cognitive symptoms in Alzheimer's disease. Neuroendocrinol Lett. 1998;19(3):111–115.
19. Miyamoto M. Pharmacology of ramelteon, a selective MT/MT receptor agonist: a novel therapeutic drug for sleep disorders. CNS Neurosci Therapeut. 2009;15(1):32–51.
20. Sanchez-Barcelo EJ, Martinez-Campa CM, Mediavilla MD. Melatonin and melatoninergic drugs as therapeutic agents: ramelteon and agomelatine, the two most promising melatonin receptor agonists. J Endocrinol. 2007;1(1):142–151.
21. Stevenson S, Bryson S, Amayke D et al. Study to investigate the absolute bioavailability of a single oral dose of ramelteon (TAK-375) in healthy male subjects. Clin Pharmacol Therapeut. 2004;1(75): P22.

22. Roth T, Seiden D, Sainati S, Wang-Weigand S, Zhang J, Zee P. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. Sleep Med. 2006;7(4):312–318.
23 American Psychiatric Association: Mood disorders; in: Diagnostic and Statistical Manual of Mental Disorders, ed 4, text revision. Washington, American Psychiatric Association 2002: 345–428.
24. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan E. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-DRDA Work Group under the auspices of Department of Health and Human Services task Force on Alzheimer's Disease. Neurol. 1984;34:939-944.
25. Folstein MF, Folstein SE, McHugh PR. Mini Mental State-A practical method of grading the cognitive state of patients for the clinician. J Psychiatr Res.1975;12(3):189-198.
26. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984, 141:1356-1364.