ORIGINAL RESEARCH PAPER

Volume-7 | Issue-2 | February-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, CROSSOVER STUDY OF THE EFFECT OF AGOMELATINE ON SACCADIC EYE MOVEMENTS IN HEALTHY VOLUNTEERS USING ELECTRO-OCULOGRAPHIC METHOD

Pharmacology

Gaddameedi Arun Jyothi* *Corresponding Author

Gaddameedi Arvind

G Ramakanth

UshaRani P

ABSTRACT

Background: Saccadic eye movements (SEM) have proved to be a valuable marker of central nervous system (CNS) function. Circadian rhythm progressively influences the saccadic eye movements. Agomelatine, a melatonergic antidepressant improves quality of sleep by resynchronization of the circadian rhythm. Hence, this study was designed to evaluate the effect and safety of single dose of Tab. Agomelatine 25 mg on saccadic eye movements in healthy human volunteers.

Methods: After approval from IEC and after taking writtern informed consent, 12 healthy subjects were randomized to receive either single dose of Tab. Agomelatine 25mg or placebo in a crossover design. Saccadic eye movements were recorded using electro-occulographic (EOG) method at 3 time points – pre-drug (baseline), 90min and 150min post drug at 10^0 - 60^0. The primary efficacy parameters were changes in saccade duration, peak saccadic velocity and latency period.

Results: In the agomelatine group, compared to baseline, at 90 and 150min post drug, there was a significant increase in saccade duration (SD) ($p<0.05$) and significant reduction in peak saccadic velocity (PSV) and latency period (LP) ($p<0.05$). No significant change was observed in latency period at 90min post drug . There were no significant changes in efficacy parameters with placebo. When agomelatine was compared to placebo at 90 min &150min post drug, SD significantly increased ($p<0.05$), PSV significantly decreased ($p<0.05$). At 150min post drug only latency period significantly decreased at 60^0($p<0.05$). Agomelatine was well tolerated.

Conclusion: Saccadic eye movement analysis provides a novel method of assessment of CNS function. The administration of single dose of Agomelatine 25mg significantly altered saccadic eye movements in healthy volunteers as determined by the electro-oculographic recording. However, further studies in larger number of subjects are required to confirm this effect.

KEYWORDS

Agomelatine, electro-oculography, saccadic eye movements

Introduction:

Agomelatine has various evidences available suggesting that disruption of the circadian rhythm is an important underlying cause of depression and insomnia, and manifestations of the abnormal circadian rhythm in depression include delayed sleep, shortened latency to rapid eye movement sleep, fragmented sleep, and early waking. Thus, normalization of circadian rhythm is a potential target in the treatment of depression. [1] Melatonin secretion exhibits a robust circadian rhythm.[6] In humans, plasma levels of melatonin begin to rise about 2 hours before habitual bedtime and remain elevated during the dark hours. The melatonin rhythm is the best peripheral index of the timing of the human circadian pacemaker. [2,3]

Two major effects of melatonin are sleep induction and phase-shifting of the circadian clock. The sleep-promoting effects are mediated by MT1 receptors. Melatonin advances the endogenous circadian rhythm in humans. [2] The phase-shifting effect of melatonin is mediated by MT2 receptors in SCN neurons. These neurons are sensitive to melatonin only during specific phases of the circadian cycle, reflecting circadian variations of melatonin receptor expression in the SCN under control by the molecular clock. [2,3]

The circadian rhythms influence progressively the saccadic eye movements. [4]Sleep deprivation for 24 h has been reported to impair peak velocity of saccades and lead to deficits of accuracy and latency. [5] SEM has proved to be a valuable marker of central nervous system (CNS) function. Saccadic eye movements are used continuously during normal visual activity and impairment is likely to have important consequences on visual acuity. [6] Peak saccade velocity is a sensitive indicator of sedation and is particularly sensitive to the sedative effects of benzodiazepines, opiates, barbiturates, carbamazepine, and ethanol. [7] Diazepam, reduces both the duration and velocity of saccadic eye movements, and increases saccade latency. [8]

Agomelatine (N-[2-(7-methoxynaphthalen-1-yl) ethyl] acetamide) belongs to a unique class of antidepressants as it is a MT1 and MT2 agonist and 5HT $_{2c}$ antagonist drug. Thus it shows both melatonergic and serotonergic modes of action and has been approved by the Drug Controller General of India (DCGI) on September 10, 2012.[9,10] Peak level in plasma is achieved 1-2 h after oral administration. The elimination half-life of drug is 2-3 h.[11] This has given rise to melatonin agonist and selective serotonin antagonist (MASSA) concept. [11] The incidence of insomnia in depression is up to 80%. [12]

Being a melatonergic agonist, agomelatine may affect the saccadic eye movement because of its proven chronobiotic (i.e. substance that adjusts the timing or reinforces oscillations of the central biological clock) action secondary to its agonist activity on melatonin receptors MT1 and MT2 in the suprachiasmatic nucleus (SCN).[13] Hence the present study was planned to determine the effects and safety profile of 25mg Agomelatine Vs placebo on saccadic eye movement using EOG [14]in healthy human volunteers.

Materials and methods:

Study subjects

Twelve healthy participants of either gender aged 18-45 yrs, who were willing to give the written informed consent and comply with study procedures, were selected for the study following a full medical history (including smoking habits), physical examination, haematological and biochemical screening, and an electrocardiogram. Volunteers were excluded if there was any evidence of hypersensitivity reactions to any active excipients of the test drug, history of migraine, and liver, cardiac, renal and any psychiatric diseases. Chronic smoking, alcoholism and history of substance abuse in last 30 days, intake of any beverages within 12 hours prior to the study and any medication, which may affect the study, taken within previous 1 week of the study were also excluded.

Study procedure

Written informed consent was taken from all the subjects after a full explanation of aims, procedures and risks of the study. The study was approved by the Institutional Ethics Committee and conducted in conformity with the Declaration of Helsinki. Three sets of practice eye

movement tests were conducted after the medical examination and prior to the test day to introduce the subjects to the test procedure and to make them familiar with the testing device. Data acquired in this training session were recorded, but not included in analysis. Alcohol, nicotine, chocolate or caffeine containing drinks were prohibited atleast 12hours prior to study day and during the study day. All the recordings were carried out during the period between 8:00 AM to 12:00 PM after a standard breakfast.

After screening for eligibility, 12 healthy human volunteers were randomized equally into 2 groups to receive either Tab. Agomelatine 25mg or identical placebo in a cross over design with a washout period of 7-10 days. EOG Recordings and VAS for sedation recordings were made immediately before (baseline), 90 min and 150min, after drug intake .Subjects were provided with standard breakfast and lunch during study day.

Saccadic eye movement analysis

Saccadic eye movement analysis was conducted as per the method standardized in the department of clinical pharmacology, NIMS. [14]

Hardware of the Electrooculo-graph

Figure 1 shows the configuration of a hardware system that obtains and stores images for measuring eye movement. The system is responsible for: Saccadic stimulus generation, EOG signal pickup and signal conditioning.

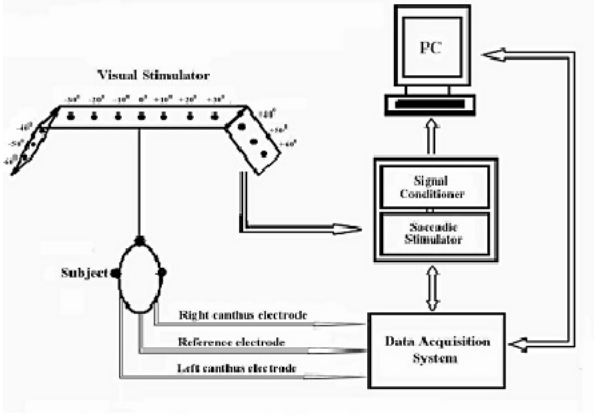


Figure 1. EOG diagnostic system

Visual analog scale (VAS) - Procedure

VAS is a subjective procedure in which subject will be instructed to mark intensity of sleep on VAS for sedation of 100mm, by a vertical line. Distance on VAS is recorded as mm [0 indicates not sleepy and 100 indicates extremely sleepy]. Three readings were taken at baseline, post 90min, and post 150min.

Statistical analysis

Data was expressed as mean ± SD. Paired t-test was used to compare the differences in Saccade duration, Peak saccade velocity & Latency period within the treatment group and to compare the differences in saccade duration, peak saccade velocity & latency period between the treatment groups (Agomelatine Vs Placebo). All statistical analyses were performed using Graph Pad Prism 5.

Results:

In our study, the saccadic eye movement was recorded in 12 healthy subjects (8 males, 4 females), with a mean age of 29.54 ± 3.98 yrs and a mean BMI of 22.4 ± 2.7 kg/m^2. SEMs at saccade amplitudes of 10^0,20^0,30^0,40^0,50^0 and 60^0 were recorded using EOG method. The mean values of saccadic eye movements (Saccade duration, Peak Saccadic velocity and Latency period) of subjects in the agomelatine group at baseline, 90 minutes post-drug and 150 minutes post-drug from 10^0 to 60^0 amplitudes are shown in Table I. The mean values of saccadic eye movements (Saccade duration, Peak Saccadic velocity and Latency period) of subjects in the placebo group at baseline, 90 minutes post-drug and 150 minutes post-drug from 10^0 to 60^0 amplitudes are shown in Table II.

Table I: Effect of Agomelatine on Saccadic Eye Movements

Agomelatine				
Time	Angular Displacement	Mean Saccade Duration (sec)	Mean Peak saccadic velocity (^{0}/sec)	Mean Latency period (sec)
0 hr	10^0	0.04 ± 0.008	256 ± 70.79	0.228 ± 0.044
	20^0	0.045 ± 0.004	444.17 ± 43.1	0.181 ± 0.022
	30^0	0.060 ± 0.003	527.34 ± 36.5	0.176 ± 0.02
	40^0	0.0697 ± 0.007	582.03 ± 67.82	0.189 ± 0.02
	50^0	0.090 ± 0.007	590.21 ± 46.16	0.195 ± 0.023
	60^0	0.093 ± 0.005	649.67 ± 40.20	0.196 ± 0.026
90 min	10^0	0.042 ± 0.008	256.02 ± 70.9	0.225 ± 0.035
	20^0	0.050 ± 0.009	394.08 ± 61.4 †	0.181 ± 0.016
	30^0	0.07 ± 0.009**§	446.56 ± 61.9 ‡,†	0.18 ± 0.014
	40^0	0.086 ± 0.006**§	483.73 ±44.01‡,†	0.178 ± 0.018
	50^0	0.099 ± 0.009**§	508.31± 49.6 ‡,†	0.194 ± 0.031
	60^0	0.01 ± 0.011**§	582.45 ±68.15‡,†	0.175 ± 0.023*
150 min	10^0	0.041 ± 0.009	251.85 ± 72.8	0.204 ± 0.024
	20^0	0.05 ± 0.005**§	371.56±34.28‡,†	0.184 ± 0.017
	30^0	0.08 ± 0.003**§	407.16 ± 85.4‡,†	0.175 ± 0.039
	40^0	0.087± 0.008**§	473.54 ± 43.4‡,†	0.174 ± 0.026¶
	50^0	0.105 ± 0.015**§	484.15 ±75.77‡,†	0.173 ± 0.033¶
	60^0	0.11 ± 0.013* *§	538.17 ±69.10‡,†	0.161 ± 0.032¶,*

Data represented as Mean ± SD

Agomelatine compared to baseline

Saccade Duration = ** p< 0.05, Peak Saccadic Velocity = ‡ ^{p}<0.05, Latency Period = ¶P<0.05,

Agomelatine compared to placebo

Saccade Duration = § p< 0.05, Peak Saccadic Velocity = † p<0.05, Latency Period = *P<0.05.

Table II: Effect of placebo on Saccadic Eye Movements

Placebo				
Time	Angular Displacement	Mean Saccade Duration (sec)	Mean Peak saccadic velocity (^{0}/sec)	Mean Latency period (sec)
0 hr	10^0	0.036 ± 0.003	280 ± 27.8	0.24 ± 0.11
	20^0	0.046 ± 0.005	441 ± 48. 6	0.17 ± 0.07
	30^0	0.06 ± 0.011	480.37 ± 83.6	0.2 ± 0.06
	40^0	0.077 ± 0.009	527.78 ± 56.1	0.19 ± 0.05
	50^0	0.085 ± 0.009	594.43 ± 79.46	0.19 ± 0.06
	60^0	0.98 ± 0.009	620.1 ± 58.56	0.19 ± 0.04
90 min	10^0	0.036 ± 0.003	282.82 ± 27.7	0.19 ± 0.1
	20^0	0.05 ± 0.009	439.85 ± 71.26	0.18 ± 0.03
	30^0	0.06 ± 0.004	492.8 ± 31.29	0.19 ± 0.05
	40^0	0.069 ± 0.007	581.54 ± 58.19	0.19 ± 0.06
	50^0	0.084 ± 0.006	593.36± 46.91	0.2 ± 0.02
	60^0	0.097 ± 0.011	628 ± 66.17	0.22 ± 0.04
150 min	10^0	0.037 ± 0.003	270.1 ± 21.92	0.21 ± 0.12
	20^0	0.049 ± 0.005	415.47 ± 45.84	0.16 ± 0.1
	30^0	0.06 ± 0.005	487.8 ± 41.4	0.18 ± 0.04
	40^0	0.073 ± 0.018	553.17± 55.70	0.19 ± 0.02
	50^0	0.088 ± 0.006	582.45 ± 68.16	0.17 ± 0.02
	60^0	0.99 ± 0.009	609.4 ± 48.79	0.2 ± 0.05

Data represented as Mean ± SD

Saccade duration:

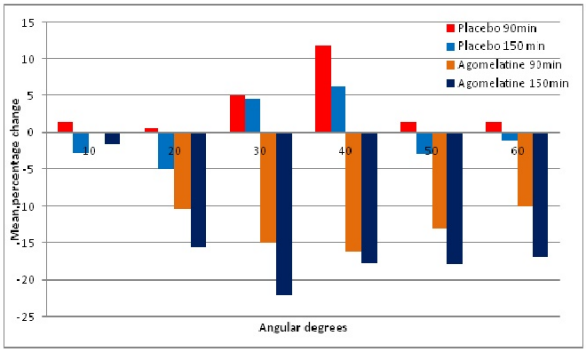
When the mean saccade duration values in the agomelatine group were compared with baseline, a significant increase in Saccade duration was observed 90min post-drug at 30^0(p=0.002), 40^0(p=0.004), 50^0(p=0.001), 60^0(p=0.001) amplitudes and 150 min at 20^0(p=0.001), 30^0(p=0.001), 40^0(p=0.003), 50^0(p=0.001), 60^0(p=0.001) amplitudes. There were no significant changes in the mean saccade duration values in placebo group.

When agomelatine was compared with placebo, a significant difference was observed in saccade duration 90min post-drug at

30^0(p=0.01), 40^0(p=0.01), 50^0(p=0.01), 60^0(p=0.04) and 150 min at 20^0(p=0.04), 30^0(p=0.01), 40^0(p=0.02), 50^0(p=0.02), 60^0(p=0.01) amplitudes..

Mean percentage change (MPC) for saccade duration between agomelatine and placebo was significant at 20^0 to 60 ^{0} post 90min and 150min of drug administration (p<0.05).

Figure 2 shows the mean percentage change of saccadic duration of agomelatine compared to placebo

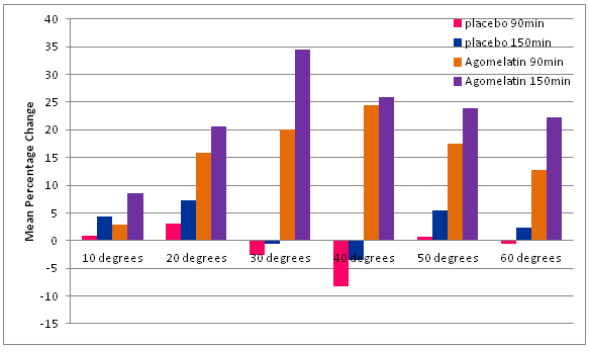


Peak saccadic velocity:
When the mean peak saccadic velocity values in the agomelatine were compared with baseline, a significant decrease in peak saccadic velocity was observed 90 min post-drug at 30^0(p=0.001), 40^0(p=0.01), 50^0(p=0.01), 60^0(p=0.01) and 150 min at 20^0(p=0.01), 30^0(p=0.002), 40^0(p=0.003), 50^0(p=0.001), 60^0(p=0.001) amplitudes.

There were no significant changes in the mean peak saccadic velocity values in placebo group. When agomelatine and placebo were compared 90 min post-drug, there was a significant difference in peak saccadic velocity at 20^0 (p=0.04), 30^0(p=0.03), 40^0(p=0.04), 50^0(p=0.002), 60^0 (p=0.05) and 150 min at 20^0(p=0.05), 30^0(p=0.03), 40^0(p=0.03), 50^0(p=0.002), 60^0(p=0.02) amplitudes.

MPC for peak saccadic velocity between agomelatine and placebo was significant at 30^0, 40^0, 50 ^{0},60^0 post 90min and 150min of drug administration (p<0.05).

Figure 3 shows the mean percentage change of peak saccadic velocity of agomelatine compared to placebo



Latency period:
Compared to baseline, a significant decrease in the mean latency period (LP) was observed 150 min post-drug at 40^0(p=0.01), 50^0(p=0.01), 60^0(p=0.001). No significant changes were observed 90min post-drug.

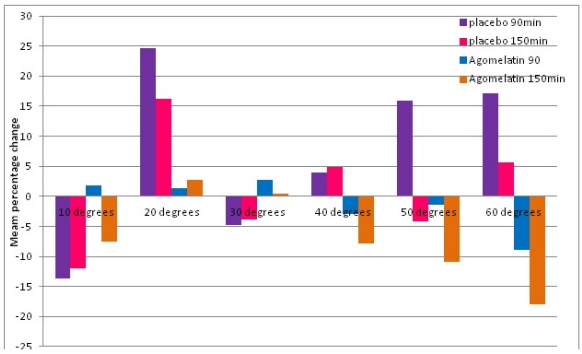
There were no significant changes in the mean latency period values in placebo group.

When compared to placebo, agomelatine showed a significant decrease in Latency period 90min post-drug at 60^0 (p<0.01) and 150 min post-drug at 60^0(p=0.02).

Mean percentage chang for latency period between agomelatine and placebo was significant at 50^0& 60^0 post 90min of drug administration (p<0.05).

After 150min there was significant difference at 60^0 between two treatment groups.

Figure 4 shows the mean percentage change of latency period of agomelatine compared to placebo.



Visual analog scale (VAS) for Sedation

The results of VAS for sedation are summarized in **Table III.** When the VAS scores for sedation of subjects in the agomelatine group were compared with baseline, a significant increase in the sedation scores were observed 90min post-drug (p=0.001) and 150min post-drug (p<0.001). However, there were no significant changes in the VAS scores for sedation in the placebo group.

When the VAS sedation scores were compared between agomelatine and placebo groups, significant differences were observed 90min post-drug (p<0.001) and 150min post-drug (p<0.001).

Table III: Visual analog scale (VAS) for sedation in agomelatine group

Agomelatine			Placebo		
Predrug	Postdrug (90min)	Postdrug (150min)	Predrug	Postdrug (90min)	Postdrug (150min)
1.75± 1.35	10. 58 ±5.16*	18.75±6.9 *	1.91±1.82	2.25±2**	2.91 ±2.38**

Data represented as Mean ± SD
Compared to baseline (p<0.001)*
Compared to placebo (p<0.001) **

Adverse effects
No adverse drug reactions (ADRs) were observed, except two subjects in the agomelatine group reported mild headache and one subject had drowsiness. In placebo group one subject reported headache. All the adverse effect resolved without any treatment.

Discussion:
The present study was conducted in 12 healthy volunteers evaluating the effect and safety of Agomelatine 25 mg on saccadic eye movements. The study population was homogenous with no significant changes in the baseline parameters.

Saccade is a quick, simultaneous movement of both eyes between two phases of fixation in the same direction. [15] This phenomenon can be associated with a shift in frequency of an emitted signal or a movement of a body part or device. Cerebellar disorders and degenerative disorders of the CNS and drug abuse e.g. antidepressants, sedatives, and anticonvulsants can often be diagnosed through saccadic testing. The 3 saccadic parameters most relevant include peak saccade velocity (PSV), saccade duration (SD) and latency period (LP). [16]In our study, the 3 saccadic eye movements were recorded using the EOG method from 10^0 to 60^0.

In healthy volunteers when the effect of agomelatine 25 mg single dose on SEMs was evaluated, there was a significant increase in SD and decrease in the PSV at post drug 90 min and 150 min from 20^0 through to 60^0, compared to baseline. Agomelatine when compared to placebo, significant increase in SD & decrease in PSV were observed at 90min and 150 min post drug. Further, it has been shown that increased SD and decreased PSV lead to saccade slowing. Such a pattern of SEM is observed with drugs like antidepressants, sedatives, anticonvulsants

and some CNS disorders.[16] In our study, Agomelatine, a melatonergic antidepressant produced the pattern of SEM that is consistent with the available evidence from the existing studies.

With regard to the latency period (LP) in our study, Agomelatine 25 mg single dose significantly decreased LP at 150 min compared to baseline from 40^0 through to 60^0. No significant changes were observed at 90 min post drug. However, when agomelatine was compared to placebo, a significant decrease in LP was observed at 90min and 150 min post drug at 60^0. Latency period is calculated from the difference in the time between target displacement and the onset of the 1^{st} saccade toward the new target position. Prolonged latency period is associated with certain disease process like basal ganglia disorders. In most instances this finding has no diagnostic significance because LP is sensitive to mental state of the subject.[16] There is no disease process that causes shortening of latency; accordingly this finding is always related to technical error or lack of cooperation.

Saccadic eye movements are progressively influenced by circadian rhythms of the body. As melatonin increases 2hrs prior to onset of sleep, it leads to decrease in peak saccadic velocity. As pointed out in a study, saccade duration increases approximately linearly with saccade amplitude, whereas PSV increases with amplitude at a decreasing rate.[17] The findings of our study correlated well with the findings of the above mentioned study.

In a study it was reported that agomelatine improved sleep continuity and quality. It normalized the distribution of slow-wave sleep and delta power throughout the night.[18] Agomelatine improves disturbed sleep–wake cycles and daytime functioning in Major depression disorder [19] and demonstrated sleep electroencephalographic changes consistent with desirable sleep architecture improvements, as well as improved subjective sleep quality within the first week of administration accompanied by an improvement in daytime alertness.[20]

In a study conducted by Raveendranadh Pilli et al , 24 healthy volunteers were given zolpidem 5mg, caffeine 500mg and placebo ,Zolpidem produced statistically significant decrease in PSV compared to placebo at all the angular displacements at 1 & 2hrs. In contrast, caffeine produced non-significant increase in PSV at all angular displacements at 1hr. Similarly latency period (LP) increased with zolpidem and decreased with caffeine compared to placebo.[14]In our study, when compared to baseline and placebo, agomelatine increased SD and reduced PSV and latency period.

In another study, there was reduction in PSV following single and repeated administration of 5 mg, 10 mg and 20 mg zolpidem. [21] A significant decrease in PSV following administration of 10 mg diazepam and 20 mg temazepam, that persisted for 9 hrs was reported in Bittencourt, P. R et al study .[22] Similarly Hopfenbeck J. R et al reported a decrease in PSV and increase in latency period following intravenous administration of diphenhydramine. [23]

In our study, agomelatine was evaluated for its sedative effect with visual analog scale for sedation. When compared with placebo, a significant sedative effect was observed with agomelatine at 90min ($p=0.001$) and at 150 min ($p<0.001$). Further, it has been shown in a study that agomelatine improved sleep continuity and quality and it normalized the distribution of slow wave sleep. [12]

In our study, agomelatine a melatonergic antidepressant produced significant sedation in VAS for sedation procedure and this is in consistent with the available evidence from the existing studies.

The safety profile of agomelatine was evaluated by recording the adverse effects observed with the drug. In our study, among 12 subjects, 2 subjects reported mild head ache, and one had drowsiness and in placebo group only one subject had headache.

Conclusion:

Saccadic eye movement analyses provides a novel method of assessment of CNS function and are progressively influenced by circadian rhythm of the body. Agomelatine, a melatonergic antidepressant, resynchronizes the circadian rhythms and thus affects saccadic eye movements. In this study, administration of single dose of agomelatine 25mg in healthy volunteers significantly increased saccade duration, decreased peak saccadic velocity and latency period from baseline and compared to placebo, suggesting its antidepressant and sedative effects. Hence, testing saccadic eye movements by the electro-oculographic recording can be used to demonstrate the antidepressant and sedative effects of agomelatine. And Electrooculograph recording can used as a tool in the early drug development studies for these class of drugs.

Reference:

1. Popoli M. Agomelatine: Innovative pharmacological approach in depression. CNS Drugs 2009; 23 (2):27-34.
2. Lack LC, Wright HR. Chronobiology of sleep in humans. Cell Mol Life Sci 2007; 64(10): 1205-15.
3 Pandi-Perumal SR, Srinivasan V, Maestroni GJ, Cardinali DP, Poeggeler B, Hardeland R. Melatonin: nature's most versatile biological signal? Febs J 2006; 273(13): 2813-38.
4. Christian Cajochen, Sat Bir S. Khalsa, James K. Wyatt, Charles A. Czeisler, Derk-Jan Dijk. EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. American Journal of Physiology – 1999; 277 (3): 640-9.
5. Fransson, P. A., Patel, M., Magnusson, M., Berg, S., Almbladh, P., & Gomez, S. Effects of 24-hour and 36-hour sleep deprivation on smooth pursuit and saccadic eye movements. Journal of Vestibular Research, 2008; 18 (4): 209-222.
6. Bittencourt PRM, Wade P, Smith AT, Richens A. The relationship between peak velocity of saccadic eye movements and serum benzodiazepine concentrations. Br J clin Pharmac 1981; 12: 523-33.
7. A, Marshall RW, Richens A. Saccadic eye movement analysis as a measure of drug effects on human psychomotor performance. Br J clin Pharmac 1984; 18: 73S-82S.
8. Aschoff JC. The effect of diazepam (Valium®) on the saccadic eye movements in man. Arch Psychiat Nervenkr 1968; 211: 325-32.
9. Medline India-Medicines Approved for marketing .Available from: http://www.medlineindia.com/list of approved drugs in 2012 India.html.
10. Martinotti G, Sepede G, Gambi F, Di Iorio G, De Berardis D, Di NicolaM, et al. Agomelatine versus venlafaxine XR in the treatment of anhedonia in major depressive disorder. J Clin Psychopharmacol2012; 32:487-91.
11. Girish MB, Bhuvana K, Nagesh Raju G, Sarala N. A novel atypical antidepressant drug : Agomelatine-A review. Int J Pharm Biomed Res 2010; 1:113-6.
12. Quera Salva MA, Hartley S, Barbot F, Alvarez JC, Lofaso F, Guilleminault C. Circadian rhythms, melatonin and depression. Curr Pharm Des 2011; 17:1459-70.
13. Giuseppe Di Iorio, M, Stefano, A,Tiziano, C ,M, Melissa, V, Federica,Cinosi Eduardo and M, Giovanni*.Antidepressants and Sleep: Neurophysiology and Clinical Correlates. current psychiatry reviews .2012;8(1):2-13(12).
14. Raveendranadh Pilli, Naidu M.U.R, Usha Rani Pingali& Ramesh Kumar Rao Takallapally, An Electrooculographic Method for the Evaluation of Psychotropic Drugs on Saccadic Eye Movements in Healthy Subjects .International Journal of Psychological Studies.2012;4(2) :75-87.
15. Cassin, B. and Solomon, S. Dictionary of Eye Terminology. 6th edition. Florida:Triad Publishing Company;1990.
16. Hain, T. Interpretation and usefulness of ocular motility testing.In: handbook of balance function testing. By; Jacobson G,Newman C and Kartush J .San diego .London : Singular publishing group ;1993. Pp.101-122.
17. Baloh, R. W., Sills, A. W., Kumley, W. E., & Honrubia, V. Quantitative measurement of saccadic amplitude, duration, and velocity. Neurology, 1975; 25(11): 1065-70.
18. Quera Salva MA, Vanier B, Laredo J, Hartley S, Chapotot F, Moulin C, et al. Major depressive disorder, sleep EEG and agomelatine: an open-label study. Int J Neuropsycho- pharmacology 2007; 10(5): 691-6.
19. Quera Salva MA, Lemoine P, Guilleminault C. Impact of the novel antidepressant agomelatine on disturbed sleep-wake cycles in depressed patients. Hum Psychopharmacol 2010; 25(3): 222-9.
20. Kupfer DJ. Depression and associated sleep disturbances: patient benefits with agomelatine. Europen Neuropsychopharmacol 2006; 16 (5): 639-43.
21. Richens, A., Mercer, A. J., Jones, D. M., Griffiths, A. & Marshall, R.W. Effects of zolpidem on saccadic eye movements and psychomotor performance: a double-blind, placebo controlled study in healthy volunteers. British Journal of Clinical Pharmacology, 1993 ;36(1): 61-65.
22. Bittencourt, P. R., Wade, P., Smith, A. T., & Richens, A. (1981). The relationship between peak velocity of saccadic eye movements and serum benzodiazepine concentrations. British journal of clinical pharmacology, 1981; 12(4):523-533.
23. Hopfenbeck, J. R., Cowley, D. S., Radant, A., Greenblatt, D. J., & Roy-Byrne, P. P. Effects of diphenhydramine on human eye movements. Psychopharmacology (Berl), 1995; 118(3): 280-286.