ORIGINAL ARTICLE

Suppression of melatonin secretion in healthy subjects with eyeglass LED delivery system

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Abstract

OBJECTIVE: Practicability remains a problem in light therapy of biological rhythm disorders. We report here the effect on melatonin secretion of a device consisting of a prototype of eyeglasses including light emitting diodes (LED) in lenses (Somnavue®).

METHODS: Light (1,200 lx) was administered in a randomised crossover design to ten healthy subjects with Somnavue® for 1 or 2 hours, Lumino® (a helmet which administers light) for 1 hour, and placebo, beginning at 01:00 h. Plasma melatonin concentrations were evaluated between 20:00–05:00 h.

RESULTS: Multiple comparisons showed differences between placebo and Somnavue® administered for one or two hours ($p<0.01$ and $p<0.05$ respectively) and Lumino® and placebo ($p<0.05$).

CONCLUSIONS: In conclusion, Somnavue® was able to suppress melatonin. The development of such a device could increase adherence with light treatment in SAD or circadian rhythm sleep disorders.

INTRODUCTION

Bright light therapy has been proposed as the treatment of choice for seasonal affective disorder (SAD) and is recommended as a first-line treatment in expert and consensus clinical guidelines (Golden *et al.* 2005). Timed light exposure is also administered in circadian rhythm sleep disorders, mainly in delayed sleep phase syndrome (DSPS); (Sack *et al.* 2007). In SAD, patients are usually asked to sit in front of a light box for at least 30 minutes each morning, sometimes for upwards of an hour. The result of a pilot study suggested that the adherence with light treatment was only 59.3% of the prescribed time, although of a similar order of magnitude to antidepressant medication adherence (Desan *et al.* 2004; Michalak *et al.* 2007). Dropout from treatment was 31.6%. In DSPS, a two hour bright light exposure (2,500 lx) can phase advance the circadian clock and improve morning alertness (Rosenthal *et al.* 1990). Again, compliance may be a significant problem since

patients, considering additional sleep to be the priority of the moment, may ignore the alarm and delay or skip the treatment (Terman and Terman 2005). Some portable devices have recently been developed, such as light visors, which are intended to increase flexibility and convenience of use. They are not discrete, however, and some of them need individual adjustment to the anatomy of the patient, and their clinical efficacy is debatable (Terman and Terman 2005). Administration of light via systems included in glasses of goggles could be an elegant solution to increase adherence with treatment. Such devices including light emitting diodes (LED) in the frame can be used to suppress or phase-shift melatonin secretion (Wright and Lack 2001; Wright *et al.* 2001; 2004; Paul *et al.* 2007). Since melatonin secretion participates in the regulation of the circadian system and is suppressed at night by bright light (Lewy *et al.*1980), suppression of this secretion can represent an objective indicator of efficacy of such devices on biological rhythms. We report here on the effect on melatonin secretion of prototype eyeglasses including LEDs in the lenses.

SUBJECTS AND METHODS

Subjects

The protocol was approved by the Ethics Committee of Hospices Civils de Lyon and the subjects gave written informed consent. Ten male subjects were recruited through advertisements in the Faculties of Medicine and Pharmacy of Lyon and were remunerated for their participation. Subjects completed the Horne and Ostberg questionnaire to determine their chronotype (Horne and Ostberg 1976), and extreme morning or evening type subjects were excluded. All potential participants took part in an extensive clinical interview including a detailed investigation of their health. These subjects of Caucasian origin were neither smokers nor strong alcohol consumers. They were within 10% of their ideal body weight and were free of any organic illness or psychiatric disorder. Especially, they were non migraineurs. Treatment with any antidepressant or hypnotic drugs was a basis for exclusion. We also excluded from the study volunteers with ocular disease, including ametropia > 5 dioptres. No abnormality of color vision and visual field was detected using suitable tests (visual field: Goldmann, Humphrey FastPac 24-2, FDT perimetry, Ishihara test, Farnsworth 28 Hue test). Associated with biomicroscopy of the anterior segment, intraocular pressure measurements and fundoscopy with blue light photography of optic nerve fibres ruled out vascular disease of the retina and glaucoma. Melatonin secretion was previously evaluated at home, in the presence of domestic light, by determination of urine 6sulfatoxy-melatonin (aMT6s), the main hepatic melatonin metabolite. Low melatonin secretors were excluded (20:00–08:00h aMT6s excretion less than 5 µg/12h). The ten selected subjects were 18–29 years old (median 22 years) at the time of exploration.

Protocol

Light was administered with Lumino® or Somnavue®. Lumino® (Schreder Inc., Ans, Belgium) is a light helmet designed for treatment of depression or sleep-wake-cycle abnormalities In a previous study, this device had showed a significant suppressive effect on plasma melatonin levels with illuminance as low as 300 lx (Claustrat *et al.* 2004). The optical block including a fluorescent lamp is individually adjusted to the head anatomy to deliver white spectrum 1,200 lx at eye level. Somnavue® (Enlightened Technologies Associates, Inc., ETAI, Fairfax VA, USA) is a portable light device comprising LEDs mounted on spectacle frames. LEDs are powered by a rechargeable battery. The placement of the fibres is in a circular pattern as shown in Figure 1. The ends of the fibres are cleaved at a 45 degree angle and coated with a compound that reflects the light from the fibres into the eyes. The diameter of the circle is approximately 20 mm and its centre is to be in line with the centre of the pupil in a forward gaze position. Because the fibres are at a slight angle to the plane of the lens, the circle of the light is radiated in a conical pattern such that it passes through the pupil and onto the retina, but remains outside the fovea in the forward gaze. In this way, subjects receive light therapy without interference with their direct vision. The units show an effective photometric illuminance of 1,200 lx, calculated at a distance of 12 mm from the corneal surface. The white spectrum at that location is produced by 6 diodes (1 blue, 470–480 nm; 2 green, 523–525 nm; 3 red, 623–644 nm) which irradiate 80 µW/cm^2 on each eye at the corneal surface. Applying FDA's substantially equivalent (SE) criteria to the Somnavue®, the device was found SE to previously cleared devices. Electro-mechanical and optical safety were previously established by the manufacturer. Eye safety in the presence of phototherapeutic light of the device was previously established by ETAI in 11 subjects who wore the Somnavue® system in the

Fig.1. Somnavue® device.

evening (20:00–22:00 h) for 14 days (ETAI, specification sheet).

The level and duration of light exposure were chosen to obtain a significant degree of melatonin suppression. Each subject was studied during four randomly assigned sessions beginning at 01:00h and separated exactly by 1 week, two sessions when they wore Somnavue® for one or two hours, one session with Lumino® for one hour and one placebo session when they wore Somnavue® or Lumino® with lights off. They wore black goggles (light transmission 11 and 12% for white and blue lights respectively) from 19:30 h to 05:00 h, except during light or placebo exposure. During the sessions performed in a room lighted below 50 lx, subjects were asked not to gaze at the source of light in the devices and were allowed to rest or to pursue activities such as reading or watching TV. They could sleep after light administration, but only in a sitting position to eliminate the influence of posture on melatonin levels (Deacon and Arendt 1994). Blood was sampled through an indwell-

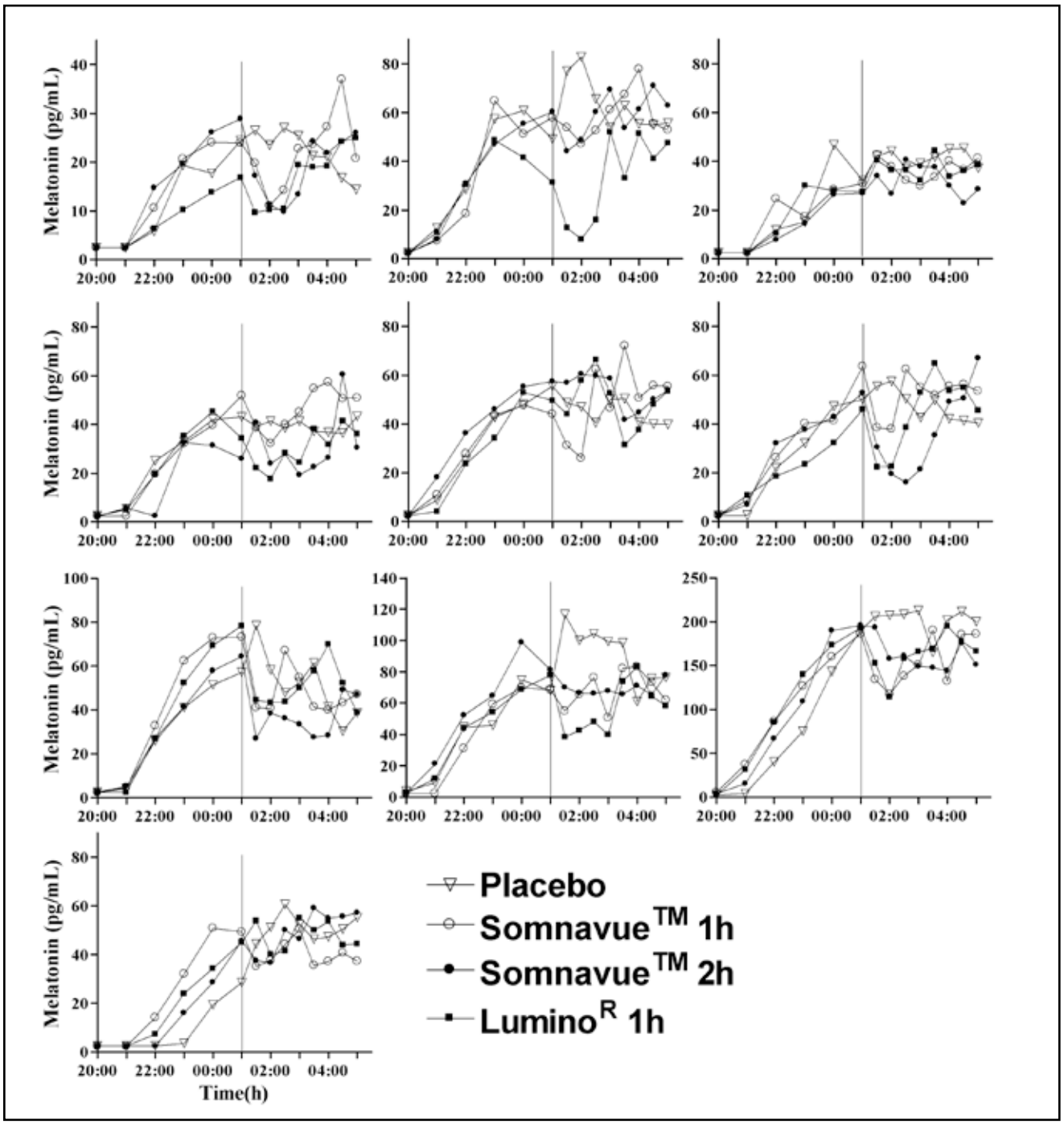

Fig. 2. Individual plasma melatonin profiles in the 10 healthy volunteers during administration of Somnavue® for 1 h or 2 h, Lumino® for 1 h or placebo.

ing catheter inserted into an antecubital vein every hour between 20:00–01:00 h and every 30 minutes between 01:00 h and 05:00 h. The IV line was kept patent with a slow drip of heparinized saline (5,000 IU heparin/l). At each sample time, 3 ml of blood was collected, immediately transferred to heparinized plastic tubes, stored at 4 °C, and centrifuged. The plasma samples were kept frozen at –20 °C until determination of concentration using a radio-immunoassay (Claustrat *et al.* 1984). The sensitivity of the assay was routinely 3 pg/ml. The intra-assay coefficients of variation were less than 7% between 30 and 200 pg/ml and the inter-assay coefficients of variation were 8.7 and 7.9% (n=18) for concentrations of 55 and 115 pg/ml, respectively. All plasmas from a same subject were simultaneously run in the same assay in order to reduce inter-assay variation.

Statistical analysis

The effects of time and light treatment were assessed by applying to placebo and light profiles a multiple analysis of variance (MANOVA) for repeated measures, including Greenhouse-Geisser corrections (SPSS®, Paris, France). Post-hoc comparisons were performed with Bonferroni-test. In addition, for each subject, we evaluated the reduction of the melatonin secretion during light and placebo sessions by calculating the surface area (Area under Curve, AUC) limited by the plasma profile between 01:00 h and 03:00 h and the line parallel to the abscissa drawn through the melatonin concentration at 01:00 h**.** AUC were negative in the presence of melatonin suppression. Taking in consideration the results of the melatonin profiles, we calculated a percentage melatonin suppression defined as [(melatonin concentration at 01:00 h (immediately prior to phototherapy) – melatonin concentration at 02:00h (minimum melatonin concentration)/ melatonin concentration at 01:00h] × 100 (Paul *et al.* 2007). Both AUC and percentage melatonin suppression data were submitted to a one-way analysis of variance (non parametric Friedman-test) followed by post-hoc comparisons with Tukey-test. Results are given as mean ± S.E.M.

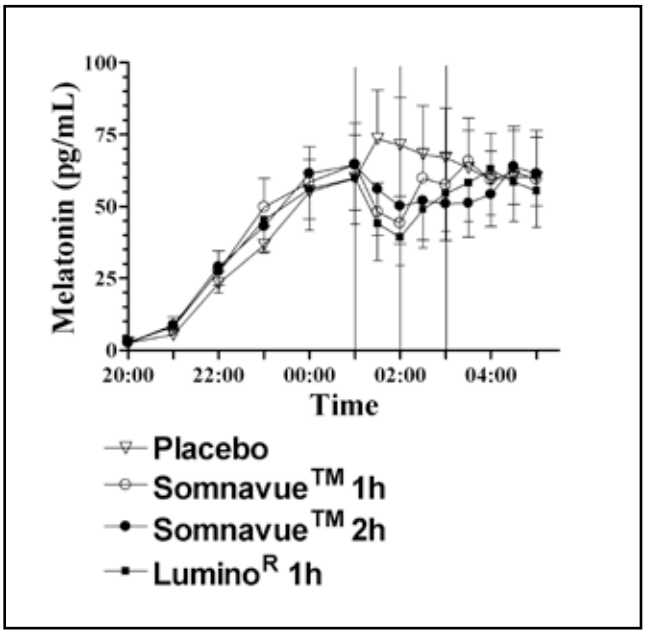

Fig. 3. Mean ± SEM plasma melatonin profiles in the 10 healthy volunteers during administration of Somnavue® for 1 h or 2 h, Lumino® for 1 h or placebo.

RESULTS

The Somnavue® device was well tolerated. The subjects were able to read or to watch TV without difficulty. There was no report of glare. No side effects, especially headache, eye or vision problems, nausea or vomiting were reported. Some subjects felt a slight sensation of warmth at the level of the bridge of the nose. Visual inspection of individual profiles showed heterogeneity of melatonin suppression (Figure 2). Mean plasma melatonin profiles are given in Figure 3. Melatonin suppression displayed a maximum at 02:00h for each device. MANOVA performed on the rough data showed a time effect ($p<0.001$, $F_{3,27}=12.63$), but no treatment effect ($p=0.84$, $F_{2,27}=0.17$) or interaction ($p=0.29$, $F_{6,27}=1.23$). For the AUC (Figure 4a), the one-way ANOVA showed a treatment effect ($p<0.01$, $F_{3,27}=3$). Multiple comparisons showed differences between placebo and Somnavue® administered for one or two hours ($p<0.01$ or $p<0.05$ respectively) and Lumino® and placebo ($p<0.05$). The results were similar for the percentage melatonin suppression (Figure 4b). The one-way ANOVA showed a treatment effect ($p<0.01$, $F_{3,27}=3$). Multiple comparisons showed differences between placebo and Somnavue® administered for one or two hours ($p<0.05$ for both) and Lumino® and placebo ($p<0.05$)

DISCUSSION

Our findings showed that goggles including LEDs which delivered a combination of 3 wavelengths and relative low illuminance were able to suppress melatonin secretion in healthy subjects. Other reports on melatonin suppression with LEDs involved monochromatic light. Paul *et al.* (2007) obtained a suppression of same order of magnitude (35%) as us with the administration of higher illuminance (2,000 lx) of monochromatic light (510 nm), whereas Wright and Lack (2001) obtained a 60–80% suppression with a 130 μW/cm² irradiance at 470–525 nm wavelengths. MANOVA performed on our raw data did not reveal any treatment effect. This could be related to poor intra-subject reproducibility and the small number of subjects included in the study. Especially, melatonin onset varied by two hours, for example in the 3 sessions of subject ten. This aspect is missed in studies involving a one-point blood sampling (Gaddy *et al.* 1993). The calculation of the AUC or percentage melatonin suppression reduced the inter-subject varia-

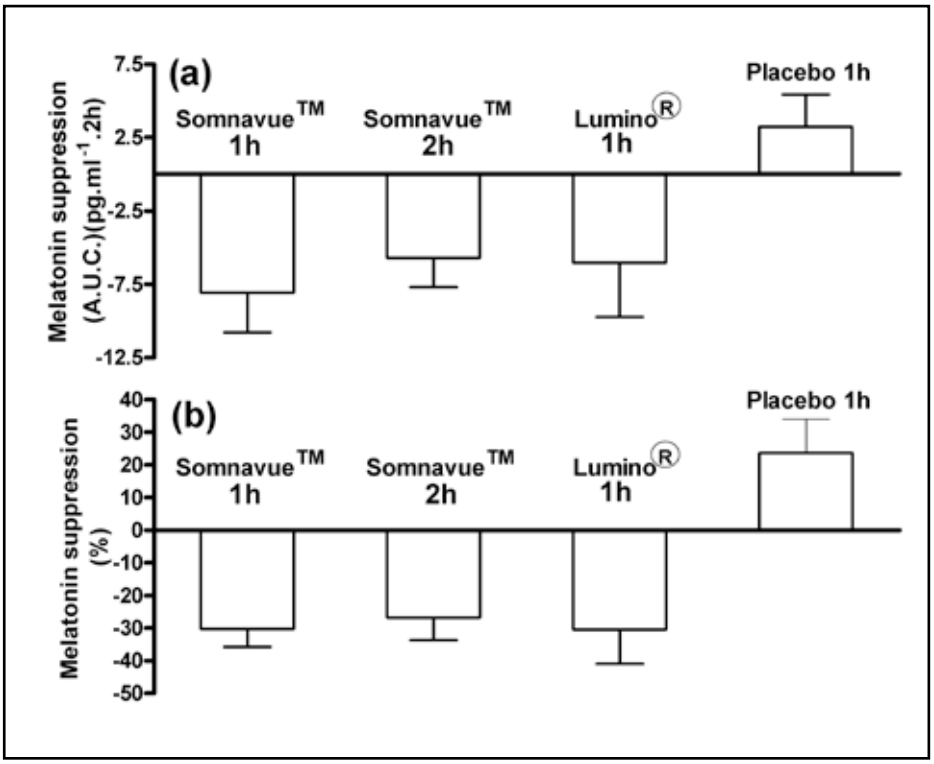

Fig. 4. Melatonin suppression (a:AUC; b: percentage) according to the light administration device or placebo. ANOVA shows a treatment effect.

tions, leading to significant results. Another subject did not display melatonin suppression with any light device. An explanation for this non-robust suppressive effect of light was that Somnavue® could not properly be adjusted. For example, in some subjects, the centre of the pupil was not in line with the centre of the pattern including the LEDs (Figure 5). In other subjects, the branches of the goggles could have been too short, with the result of a plane including LEDs which was no longer vertical, perpendicular to the optical axis. Both adjustable between-eye space and branches could improve the ergonomics of Somnavue®, producing more reliable melatonin suppression. Such technical aspects are not reported in the evaluation of devices in phototherapy. Another reason why some subjects might not show melatonin suppression could be prior light history, for example excessive outdoor light exposure between sessions (Hébert *et al.* 2002).

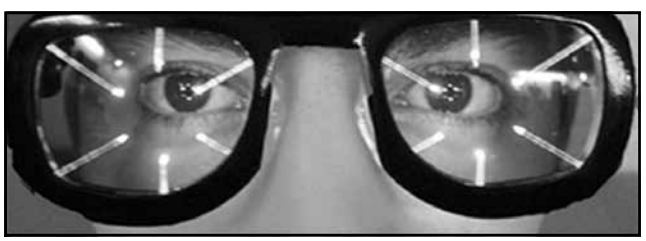

Fig. 5. Example of a subject wearing Somnavue®. The centre of the pupil is not in line with the centre of the pattern including the LEDs.

Wavelengths can be easily modulated with this kind of device. This is of interest since the administration of poly- vs monochromatic light remains an important research area in applied light therapy. Short wavelengths are more efficient on melatonin suppression and phase shifting. Additional wavelengths leading to composite bright light, however, increase melatonin suppression (Revell and Skene 2007). Also, LED spectacles presenting monochromatic light of 510 nm bring discomfort (Paul *et al.* 2007). Finally, variable combinations of monochromatic lights to simulate natural dawn or dusk lighting or "blue-enriched" light could reinforce the efficacy of treatment (Terman and Terman 2006; Terman 2008). There are retinal damage possibilities, however, with pure blue.

In conclusion, such a LED device with some improvements should be tested in more naturalistic conditions, for example in circadian rhythm disorders. It could favour the completion of controlled trials in these fields, since light levels and wavelengths can be easily modified. Due to flexibility and convenience of use, wearing of this device could reinforce efficiency and adherence with light treatment. Finally, the feasible inclusion of LED in optical lenses reinforces interest in this device.

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