CASE REPORT

Psychiatry and Clinical Psychopharmacology 2021;31(2):241-244
DOI:10.5152/pcp.2021.21234

Melatonin Related Acneiform Lesions: A Case Report and Potential Mechanism

Baris Sancak[1], Zeynep Ozdemir[2], Ozan Ozcan[3], Erkan Acar[4]

[1]Department of Psychiatry, Acıbadem Mehmet Ali Aydinlar University School of Medicine, Atakent Hospital, Istanbul, Turkey; [2]Department of Neurology, Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Istanbul, Turkey; [3]Department of Biochemistry, Marmara University School of Dentistry, Istanbul, Turkey; [4]Department of Neurology, Acıbadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Turkey

ABSTRACT

Melatonin (MLT) is a hormone secreted by the pineal gland according to the circadian rhythm, which is generated by the suprachiasmatic nucleus. The sleep-promoting effect of exogenous MLT is used to treat sleep disorders. The most common side effects reported are headache, somnolence, palpitations, and abdominal pain. Some studies showed dermatological side effects with the use of exogenous MLT, but did not list the specific symptoms. In this article, we describe a case of facial acne occurring after the use of MLT, which is generally known to have protective and healing effects on the skin, and the potential mechanism of this surprising side effect.

ARTICLE HISTORY

Received: 3 March, 2021
Accepted: 20 April, 2021

KEYWORDS: Acneiform lesions, depression, insomnia, melatonin, sleep disorders

INTRODUCTION

Melatonin (MLT) is a hormone secreted by the pineal gland, affected by the suprachiasmatic nucleus in the hypothalamus according to the circadian rhythm. It is known to have a sleep-promoting effect.[1] MLT exerts its effects in the central nervous system (CNS) and peripheral tissues through the MT1 and MT2 receptors. It is thought that it plays a role in increasing sleep duration by inhibiting neuronal firing, especially by activation of MT1 receptors in the suprachiasmatic nucleus.[2] After it was demonstrated that taking MLT exogenously in low doses has a sleep-enhancing effect, it has been used more widely in the treatment of sleep disorders.[3] Currently, it is seen as a safer and more natural product than other drugs used for sleep regulation, therefore various doses with MLT are sold as supplements without a prescription.[4]

Despite its widespread use, existing studies do not provide strong evidence regarding the place of MLT in insomnia treatment.[5] It appears that it has no or only minimal effect on sustained sleep and overall sleep quality,[3] except for controlled studies showing that it reduces sleep latency in patients aged 55 years and older.[6] The variation in MLT doses (0.3-80 mg), selected patient groups (different age groups, patients or healthy volunteers, presence of comorbidities) and measurement methods (polysomnography, actigraphy, scales) make the results of present studies more questionable.[3,5] However, the benefit of MLT use is clearer in circadian rhythm disorders caused by jetlag and shift-based work.[7]

One of the reasons for MLT's frequent use is its safety even at high doses and its relatively low side effect profile, although it is not recommended for the treatment of insomnia.[8] Although no serious side effects have been described in the studies, the most common side effects have been reported as headache, somnolence, palpitations, and abdominal pain.[9] It has been reported that MLT, which is generally known to have protective and healing effects on the skin, might have rare side effects related to skin tissue.[4,10] In this article, we describe a case of facial acne occurring during the use of MLT and the potential mechanism of this surprising side effect.

CASE PRESENTATION

In January 2020, A 33-year-old female patient presented to the psychiatry outpatient clinic with complaints of unhappiness, anhedonia, fatigue, and poor concentration for 1 month. She had no known history of chronic disease or additional medication use. In the mental state examination, the patient was conscious, cooperative, orientated, and psychomotor retarded. She had depressed affect, dysphoric mood and partially poor self-care. The Beck Depression Inventory score was 23. The patient was

Corresponding author: Baris Sancak, e-mail: barissancak@gmail.com

Cite this article as: Sancak B, Ozdemir Z, Ozcan O, Acar E. Melatonin related acneiform lesions: A case report and potential mechanism. *Psychiatr Clin Psychopharmacol*. 2021; 31(2): 241-244.

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

diagnosed with major depression and it was learned that she had received fluoxetine treatment 3 years earlier with the same diagnosis. At the end of the first year, the treatment had been terminated due to complete remission. Therefore, the patient was started on fluoxetine 20 mg/day as treatment, which she had benefited from in the past. One week later, the patient started to use MLT 3 mg/day due to insomnia characterized by prolonged sleep latency and frequent awakenings. Since the patient felt sleepy during the day, a neurology consultation was requested to assess her for sleep disorders. Recommendations on sleep hygiene were made by the neurologist, no drug change was made because she had benefited from fluoxetine previously, and the self-initiated MLT was continued at the same dose.

In the second week of the combined selective serotonin reuptake inhibitor (SSRI) and MLT treatment, acneiform eruptions, which appeared cystic in some places, were observed, especially on the lower face (Figure 1). The patient had not had any similar complaints since having acne vulgaris in her high school years, 15 years ago. Routine tests and hormonal profiles were measured in the patient, who had no history of oral contraceptive usage. Complete blood count, lipid profile, thyroid-stimulating hormone, and free T3-T4 levels were normal. Follicle-stimulating hormone, luteinizing hormone, prolactin (PRL), total and free testosterone, sex hormone-binding globulin (SHBG), 17-OH progesterone, and dehydroepiandrosterone sulfate (DHEAS) were within normal limits on the third day of menstruation. Since skin complaints caused a significant increase in depressive complaints, the patient was followed up closely with dermatology and was started on 10 mg/day isotretinoin, increased up to 30 mg/day with liver enzyme monitoring. However, no regression was observed in the skin lesions and the depressive complaints progressed. In the retrospective evaluation of the patient, it was observed that there was no change except for starting on MLT during the period when the lesions initiated. Therefore, the isotretinoin and MLT treatments, which she had been following regularly for 2 months, were stopped. The acneiform lesions, which had increased for months, regressed dramatically after the cessation of MLT. The treatment was continued with fluoxetine 20 mg/day.

Written informed consent was obtained from the patient for publication of this paper and the accompanying image.

MAIN POINTS

- MLT is a drug that is widely used all over the world due to its low side effect profile, and is known to be effective especially in older people.
- Although the use of exogenous MLT is considered safe, attention should be paid to potential side effects.
- Since MLT is part of the complex hormonal system, more research needs to be done on its complex effects on the body.

Figure 1. Acneiform lesions after melatonin usage.

DISCUSSION

MLT is a sleep-regulating hormone, which is also thought to be an antioxidant and cytoprotective agent. Its topical usage is also becoming widespread in the cosmetics industry.[11] There are studies showing that exogenous MLT preparations may be beneficial in cancer, skin diseases, hypertension, diabetes mellitus, and diseases of the gastrointestinal system.[7] Randomized, double-blind, placebo-controlled side effect studies on MLT are very limited, despite it having been used safely for many years with generally positive results.[7] Additionally, the effects of MT1 and MT2 receptors in peripheral systems are still being investigated.[12] A comprehensive meta-analysis has shown that the side effects associated with the use of MLT vary significantly and unique side effects can be seen. The possibility of dermatological side effects has been previously reported.[4]

The effects of SSRI drugs in treating sleep disorders accompanying depression are quite limited, although they are the first-line treatment for major depressive disorder and provide significant improvement in many symptoms. They have been shown to present a significant benefit in treating sleep disturbance when combined with MLT.[13] In our case, MLT was preferred by the patient because of its easy accessibility, and continued to be used by the doctor she consulted with because it was found to be safe and effective. Since MLT is generally thought to have a protective effect on the skin,[10] it was not suspected to be related to facial acne in our case, although acne appeared immediately after using it. However, lesions that occur with the initiation of MLT and regress upon its discontinuation support this connection. Furthermore, the Naranjo causality assessment scale score for adverse drug

reactions is 6 points, therefore the adverse reaction is likely to be caused by the MLT.[14]

It may be useful to consider the effects of MLT in the neuroendocrine system to investigate the mechanism of precipitating acneiform skin lesions. MLT is considered to be one of the hormones that control PRL release in women. An increase in MLT release has been directly associated with PRL release.[15] Oral MLT use has also been shown to increase PRL levels.[4] In addition, MLT may contribute to the increase of PRL indirectly by inhibiting dopamine release through the MT2 receptor.[16] MLT also increases thyroid releasing hormone (TRH)-induced PRL synthesis in women with normal menstrual cycles.[17] Excessive sebum production due to androgen hormone-mediated stimulation of the sebaceous glands and blockages of the follicles due to abnormal keratinization are among the factors leading to the formation of acneiform lesions.[18] It is known that PRL can increase the level of dihydrotestosterone by increasing 5α-reductase activity and consequently can cause sebocyte proliferation, sebum production, and hyperkeratinization in individuals with receptor sensitivity.[19] The fact that there was no significant increase in androgens in hormone tests performed in our case suggests that partial changes may be sufficient for acne formation in women sensitive to hormonal changes at the receptor level. Our patient's history of acne in her high school years can be seen as a suggestion of her sensitivity to this condition.

The direct effects of MLT on androgens have generally been studied in women with polycystic ovary syndrome (PCOS). It has been shown that regular use of 5 mg/day MLT for 12 weeks leads to a decrease in testosterone levels in women with PCOS.[20] Another study showed a decrease in androgen levels, but no change in PRL levels, with MLT treatment at 1 mg/day for 6 months in women with PCOS.[21] TRH-induced PRL levels were found to be significantly higher with MLT (2 mg) administration in women with normal menstrual cycles.[17] These results may suggest that MLT acts as a regulator for androgen, with a lowering effect at high levels, but a partial enhancement effect at low or normal levels. Additionally, the different MLT doses used in the studies may lead to significant differences in the results obtained.

CONCLUSION

This case report represents a patient with acneiform lesions after MLT use and the potential mechanism of this side effect. To the best of our knowledge, there is no case in the literature describing facial acneiform lesions after MLT usage. Exogenous MLT use is common, and is considered safe and effective as a hormone-based treatment that has been known for many years. However, its benefits on sleep and its side effect profile have not been adequately elucidated by controlled studies. For example, studies on the hormonal effects of MLT on healthy women are quite insufficient. There is limited information on the effects of MT1 and MT2 receptors in specific tissues. A meta-analysis showed dermatological side effects with the use of MLT, but did not specifically state the nature of the side effects.[4] For these reasons, up-to-date and comprehensive research should be done. When this topic is searched using internet search engines, we encounter anecdotal cases of patients reporting acne complaints after the use of MLT, but the lack of cases in the literature suggests that the side effects seen in people with receptor sensitivity may often be overlooked. We think that it is important to conduct more comprehensive studies on the peripheral effects of MLT, as well as its effects on the CNS.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – B.S., Z.O., O.O., E.A.; Design - B.S., Z.O., O.O., E.A.; Supervision - B.S., Z.O., O.O., E.A.; Literature Search - B.S., Z.O., O.O., E.A; Writing - B.S., Z.O., O.O., E.A.; Critical Reviews - B.S., Z.O., O.O., E.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Kennaway DJ, Wright H. Melatonin and circadian rhythms. *Curr Top Med Chem*. 2002;2:199-209. [CrossRef]
2. Dubocovich ML. Melatonin receptors: role on sleep and circadian rhythm regulation. *Sleep Med*. 2007;8:34-42. [CrossRef]
3. Brzezinski A, Vangel MG, Wurtman RJ et al. Effects of exogenous melatonin on sleep: A meta-analysis. *Sleep Med Rev*. 2005;9:41-50. [CrossRef]
4. Foley HM, Steel AE. Adverse events associated with oral administration of melatonin: A critical systematic review of clinical evidence. *Complement Ther Med*. 2019;42:65-81. [CrossRef]
5. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13:307-349. [CrossRef]
6. Wade AG, Crawford G, Ford I et al. Prolonged release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response. *Curr Med Res Opin*. 2011;27:87-98. [CrossRef]
7. Rivara S, Pala D, Bedini A, Spadoni G. Therapeutic uses of melatonin and melatonin derivatives: a patent review (2012-2014). *Expert Opin Ther Pat*. 2015;25:425-441. [CrossRef]
8. Andersen LPH, Gögenur I, Rosenberg J, Reiter RJ. The safety of melatonin in humans. *Clin Drug Investig*. 2016;36:169-175. [CrossRef]
9. Costello RB, Lentino C V, Boyd CC et al. The effectiveness of melatonin for promoting healthy sleep: a rapid

evidence assessment of the literature. *Nutr J*. 2014;13:106. [CrossRef]
10. Slominski AT, Hardeland R, Zmijewski MA et al. Melatonin: a cutaneous perspective on its production, metabolism, and functions. *J Invest Dermatol*. 2018;138:490-499. [CrossRef]
11. Milani M, Puviani M. Anti-aging efficacy of melatonin-based cream: clinical and instrumental skin evaluation. *Cosmetics*. 2018;5:60. [CrossRef]
12. Liu J, Clough SJ, Hutchinson AJ et al. MT1 and MT2 melatonin receptors: A therapeutic perspective. *Annu Rev Pharmacol Toxicol*. 2016;56:361-383. [CrossRef]
13. Dolberg OT, Hirschmann S, Grunhaus L. Melatonin for the treatment of sleep disturbances in major depressive disorder. *Am J Psychiatry*. 1998;155:1119-1121. [CrossRef]
14. Naranjo CA, Busto U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245. [CrossRef]
15. Kirby AW, Clayton M, Rivera P, Comperatore CA. Melatonin and the reduction or alleviation of stress. *J Pineal Res*. 1999;27:78-85. [CrossRef]
16. Dubocovich ML, Rivera-Bermudez MA, Gerdin MJ, Masana MI. Molecular pharmacology regulation and function of mammalian melatonin receptors. *Front Biosci*. 2003;8:d1093-d1108. [CrossRef]
17. Terzolo M, Piovesan A, Osella G et al. Exogenous melatonin enhances the TRH-induced prolactin release in normally cycling women: a sex-specific effect. *Gynecol Endocrinol*. 1991;5:83-94. [CrossRef]
18. Ebede TL, Arch EL, Berson D. Hormonal treatment of acne in women. *J Clin Aesthet Dermatol*. 2009;2:16-22. [CrossRef]
19. Okechukwu Chukwu E, Juliet Ifeoma O, Chia T. Comparative study of prolactin levels in acne and non-acne individuals Among students of College of Health Sciences, Nnamdi Azikiwe University, Nnewi, Nigeria. Nnamdi Azikiwe University, Nnewi, Nigeria. *Int J Biomed Eng Clin Sci*. 2017;3:25. [CrossRef]
20. Jamilian M, Foroozanfard F, Mirhosseini N et al. Effects of melatonin supplementation on hormonal, inflammatory, genetic, and oxidative stress parameters in women With polycystic ovary syndrome. *Front Endocrinol (Lausanne)*. 2019;10:273. [CrossRef]
21. Tagliaferri V, Romualdi D, Scarinci E et al. Melatonin treatment may Be able to restore menstrual cyclicity in women With PCOS: a pilot study. *Reprod Sci*. 2018;25:269-275. [CrossRef]