Night-time exogenous melatonin administration may be a beneficial treatment for sleeping disorders in beta blocker patients

Auda Fares

Department of Internal Medicine, S. Johannes Hospital, Germany
Address for correspondence: *Dr. Auda Fares, Department of Internal Medicine, Albert-Schlangen Str. 36 50181, Bedburg, Germany. E-mail: audafares@yahoo.com*

ABSTRACT

Sleep disorders are the common side effects of beta blockers. Beta blockers have been shown to reduce the production of melatonin via specific inhibition of adrenergic beta1-receptors. Exogenous melatonin, taken in the evening as a supplement, could reduce the central nervous system (CNS) side effects (sleep disorder) associated with beta-adrenergic receptor blockers as well as the potential risk associated with reduction of the melatonin synthesis.

Key words: Beta blockers, hypertension, melatonin

INTRODUCTION

Beta-adrenergic receptor blockers are an important class of drugs in the management of patients with cardiovascular diseases. Incidence of both acute and chronic heart diseases systematically is age dependent.[1] Beta blockers often are not well tolerated, and the compliance rates with these medications are dismal. In a meta-analysis of randomized controlled trials, the risk of treatment withdrawal was 80% and 41% greater with beta blockers compared with diuretics and renin–angiotensin–aldosterone system (RAAS) blockers, respectively.[2] In contrast, melatonin concentrations in serum, as well as the urinary levels of its main metabolite, 6-sulfatoxymelatonin, are lower in older, when compared to the values observed in younger population.[3] Extensive epidemiological evidence and experimental animal studies suggest that melatonin exerts certain effects upon the cardiovascular system. The presence of vascular melatoninergic receptors has been demonstrated; these receptors are functionally associated with either vasoconstrictor or vasodilatory effects of melatonin.[4] Synthesis and release of melatonin are stimulated by norepinephrine via $beta_1$-adrenoceptors and this process is further potentiated by stimulation of $alpha_1$-adrenoceptors.[5] Beta blockers have been shown to reduce the production of melatonin via specific inhibition of beta-1 adrenergic receptors. Results of two placebo-controlled studies of hypertensive patients, investigating the relationship between beta blocker induced central nervous system (CNS) side effects and the nightly urinary excretion of melatonin, demonstrated that the CNS side effects (sleep disorder, nightmares) during beta blockade are related to a reduction of melatonin levels.[6] Similar findings have been found in case–control study of six patients with nightmares and hallucinations during treatment with beta-adrenoceptor blocking agents compared to six control patients with similar diagnoses and treatment but without such symptoms of the CNS. Nightly melatonin excretion was lower in all cases with nightly CNS symptoms than in the control patients.[7] Since sleep disturbances are common side effects of beta blockers and lower nocturnal melatonin levels might be the reason for this disorder, nighttime exogenous administration of melatonin might avoid this well-known side effect of beta blockers.

Access this article online

Quick Response Code:

Website: www.jcdronline.com

DOI: 10.4103/0975-3583.85261

MELATONIN AND HYPERTENSION

The involvement of melatonin in the regulation of arterial

blood pressure and heart rate has been implicated in several studies.[8,9] Melatonin administration has been shown to induce a hypotensive effect in both normotensive[7] and spontaneously hypertensive rats.[10,11] A lowering of arterial blood pressure has also been reported from an uncontrolled study on essential hypertensive patients.[12] A crossover, placebo-controlled study evaluating the effects of the evening intake of melatonin by young and healthy normotensive subjects[13] showed a mild hypotensive effect during the whole 24-hour period, with a concomitant heart rate lowering during the diurnal hours. In another crossover study, 16 men with essential hypertension given melatonin for 3 weeks, 1 hour before sleep onset, exhibited reduced nocturnal systolic and diastolic blood pressures by 6 and 4 mm Hg, respectively.[14] Pinealectomy enhances the vascular reactivity to vasoconstrictive agents,[15] which can be reversed by melatonin.[16] The mechanisms whereby melatonin influences blood pressure could involve any of the following: (i) a direct effect on neural centers governing cardiovascular status; (ii) reduction in catecholamine concentrations; (iii) relaxing smooth muscle in blood vessels; and (iv) antioxidative actions. The ability of melatonin to modulate blood pressure may be a result of both receptor-mediated and receptor-independent processes.

MELATONIN AND DRUG INTERACTION

Several studies have assessed the possible interaction of melatonin with other drugs on human subjects. One study reported that the non-selective beta blocker (carvedilol) and calcium channel blockers (Verapamil) do not decrease nocturnal melatonin production,[17] while another study showed that chronic evening ingestion of melatonin in hypertensive patients, well controlled by nifedipine gastrointestinal therapeutic system (GITS), induces a BP increase and a heart rate acceleration. Kinetic or pharmacodynamic interaction between melatonin and nifedipine is able to impair the antihypertensive efficacy of the calcium channel blocker.[18] This study suggests that the pineal hormone might interfere with calcium channel blocker therapy. Another study revealed that combination of angiotensin II receptor antagonist (losartan) and melatonin reduced BP more noticeably than losartan alone.[19] Recently, this group also showed that combination of moxonidine and melatonin is more effective on hemodynamic parameters in patients with arterial hypertension than moxonidine alone.[20]

CARDIOPROTECTIVE EFFECTS OF MELATONIN

Melatonin has been shown to have anti-anginal and anti-ischemic effects, to improve the contractile function following myocardial ischemia-reperfusion and also to act against oxidative damage induced by other free radical generating agents.[21,22] Recent evidence reveals that the patients with coronary heart disease, especially those with higher risk of cardiac infarction and/or of sudden death, have a low melatonin production rate. It has also been reported that people with high levels of low-density lipoprotein (LDL)-cholesterol have low levels of melatonin. It has been shown that melatonin suppresses the formation of cholesterol, reduces LDL accumulation in serum,[23] and modifies fatty acid composition of rat plasma and liver lipids.[24] However, the effects of a therapy modulating the melatoninergic system on cardiovascular hemodynamics and rhythmicity under several physiopathological conditions need to be further explored, together with the possible impact on cardiovascular morbidity and mortality.[4]

INFLUENCE OF MELATONIN ON COGNITIVE AND SLEEPING

Several studies have shown that the sleep patterns in elderly insomniacs are improved by the administration of 2 mg of melatonin.[25] A recent study has shown the positive effects of administration of 0.3 mg of melatonin in the late evening on sleep pattern in older people.[26] In one placebo-controlled crossover study of 10 elderly subjects with mild cognitive impairment, treatment with 6 mg of melatonin led to improve sleep, memory, and mood in the elderly.[27] Melatonin administration at a dose of 1 mg nightly may be effective in improving certain aspects of cognitive functioning and subjective reports of sleep quality in elderly subjects. It may prove to be a useful therapeutic agent in the treatment of age-related cognitive decline. Another intriguing aspect of the melatonin–sleep relationship is the effect of melatonin on dream quality and content. One study reported that oral administration of 250 mg of melatonin facilitated subjects' dreaming and increased the number of rapid eye movements during REM sleep.[28] Another study showed an increase in dreaming or the occurrence of more vivid dream after ingesting 0.3 mg dose of melatonin.[27]

POTENTIAL RISK ASSOCIATED WITH MELATONIN DEFICIENCY

Melatonin deficiency may be a critical starting point for the degenerative processes leading to cellular pathology and oncogenesis. Several studies have demonstrated a link between decreased melatonin synthesis and cancer. One study reported that women with breast cancer have lower levels of melatonin than those without the disease. Laboratory experiments indicate that lower levels of melatonin stimulate the growth of breast cancer cells.[29] Another study revealed that colorectal cancer patients had

lower plasma levels of melatonin than healthy control subjects, suggesting a possible link between low melatonin levels and the enhanced development of colorectal cancer in humans.[30,31] Recently, melatonin has been implicated in the pathogenesis and clinical course of multiple sclerosis. When melatonin levels decline, an exacerbation of MS symptoms is seen.[32] In another study, a significant correlation between melatonin deficiency and endometrial cancer was found.[33] Melatonin is reduced by two thirds in patients with prostate cancer as compared with those who have benign prostate disease.[34] Therefore, a relative melatonin deficiency at the cellular level, induced by beta blockers, might increase the cancer risk. Furthermore, beta-adrenoceptor blockers, which depress melatonin secretion, exert immunosuppressive effects when given in the evening. Exogenous melatonin reverses beta blocker induced immunosuppression and enhances immune parameters in animals.[34]

CONCLUSION

Exogenous melatonin taken in the evening as a supplement could reduce the CNS side effects (sleep disorder) associated with beta-adrenergic receptor blockers as well as the potential risk associated with reduction of the melatonin synthesis. However, the optimal use of melatonin in hormone replacement therapy requires that the patient recieve the correct dose at the proper time. A lack of documented negative side effects does not mean an absence of such effects. Long-term clinical and experimental studies are needed to address this important question.

REFERENCES

1. Altun A, Ugur-Altun B. Melatonin: Therapeutic and clinical utilization. Int J Clin Pract 2007;61:835-45.
2. Bradley HA, Wiysonge CS, Volmink JA, Mayosi BM, Opie LH. How strong is the evidence for use of beta-blockers as first-line therapy for hypertension?Systematic review and meta-analysis. J Hypertens 2006;24:2131-41.
3. Sewerynek E. Melatonin and the cardiovascular system. Neuro Endocrinol Lett 2002;23 Suppl 1:79-83.
4. Scalbert E, Guardiola-Lemaître B, Delagrange P. Melatonin and regulation of the cardiovascular system. Therapie. 1998;53:459-65.
5. Brismar K, Hylander B, Eliasson K, Rössner S, Wetterberg L. Melatonin secretion related to side-effects of beta-blockers from the central nervous system. Acta Med Scand 1988;223:525-30.
6. Brismar K, Mogensen L, Wetterberg L. Depressed melatonin secretion in patients with nightmares due to beta-adrenoceptor blocking drugs. Acta Med Scand 1987;221:155-8.
7. Harlow HJ. Influence of the pineal gland and melatonin on blood flow and evaporative water loss during heat stress in rats. J Pineal Res 1987;4:147-59.
8. Paulis L, Simko F. Blood pressure modulation and cardiovascular protection by melatonin: Potential mechanisms behind. Physiol Res 2007;56:671-84.
9. Forman JP, Curhan GC, Schernhammer ES. Urinary melatonin and risk of incident hypertension among young women. J Hypertens 2010;28:446-51.
10. Kawashima K, Miwa Y, Fujimoto K, Oohata H, Nishino H, Koike H. Antihypertensive action of melatonin in the spontaneously hypertensive rats. Clin Exp Hypertens 1987;9:1121-31.
11. Laflamme AK, Wu L, Foucart S, de Champlain J. Impaired basal sympathetic tone and α1-adrenergic responsiveness in association with the hypotensive effect of melatonin in spontaneously hypertensive rats. Am J Hypertens 1998;11:219-29.
12. Birau N, Peterssen U, Meyer C, Gottschalck J. Hypotensive effect of melatonin in essential hypertension. IRCS Med Sci 1981;9:906
13. Lusardi P, Preti P, Savino S, Piazza E, Zoppi A, Fogari R. Effect of bedtime melatonin ingestion on blood pressure of normotensive subjects. Blood Press Monit 1997;2:99-103.
14. Sheer FA, van Montfrans GA, van Someren EJ, Mairuhu G, Buijs RM. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. Hypertension 2004;43:192-7.
15. Cunnane SC, Manku MS, Oka M, Horrobin DF. Enhanced vascular reactivity to various agents following pinealectomy in the rats: Role of melatonin. Can J Physiol Pharmacol 1980;58:287-93.
16. Holmes SV, Sudgen D. The effect of melatonin on pinealectomy-induced hypertension in the rat. Br J Pharmacol 1976;56:360-4.
17. Stoschitzky K, Sakotnik A, Lercher P, Zweiker R, Maier R, Liebmann P, *et al*. Influence of beta-blockers on melatonin release. Eur J Clin Pharmacol 1999;55:111-5.
18. Lusardi P, Piazza E, Fogari R. Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: A 24-hour study. Br J Clin Pharmacol 2000;49:423-7.
19. Esquifino AI, Pandi-Perumal SR, Cardinali DP. Circadian organization of the immune response: A role for melatonin. Clin Appl Immunol 2004;4:423-33.
20. Zaslavskaia RM, Komarov FI, Shakirova AN, Teĭblium MM, Akhmetov KZ. Effect of moxonidine monotherapy and in combination with melatonin on hemodynamic parameters in patients with arterial hypertension. Klin Med (Mosk) 2000;78:41-4.
21. Zaslavskaya RM, Lilitsa GV, Dilmagambetova GS, Halberg F, Cornélissen G, Otsuka K, *et al*. Melatonin, refractory hypertension, myocardial ischemia and other challenges in nightly blood pressure lowering. Biomed Pharmacother 2004;58 Suppl 1:S129-34.
22. Reiter RJ, Manchester LC, Fuentes-Broto L, Tan DX. Cardiac hypertrophy and remodelling: Pathophysiological consequences and protective effects of melatonin. J Hypertens 2010;28 Suppl 1:S7-12.
23. Koziróg M, Poliwczak AR, Duchnowicz P, Koter-Michalak M, Sikora J, Broncel M. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. J Pineal Res 2011;50:261-6.
24. Sewerynek E. Melatonin and the cardiovascular system. Neuro Endocrinol Lett 2002;23 Suppl 1:79-83.
25. Garfinkel D, Laudon M, Nof D, Zisapel N. Improvement of sleep quality in elderly people by controlled-release melatonin. Lancet 1995;346:541-4.
26. Wurtman RJ, Zhdanova I. Improvement of sleep quality by melatonin. Lancet 1995;346:1491.
27. Zhdanova IV, Wurtman RJ, Balcioglu A, Kartashov AI, Lynch HJ. Endogenous melatonin levels and the fate of exogenous melatonin: Age effects. J Gerontol A Biol Sci Med Sci 1998;53:B293-8.
28. Antón-Tay F. Melatonin: Effects on brain function. Adv Biochem Psychopharmacol 1974;11:315-24.
29. Kerenyi NA, Pandula E, Feuer GM. Oncostatic effects of the pineal gland. Drug Metabol Drug Interact 1990;8:313-9.
30. Vician M, Zeman M, Herichova I, Jurani M, Blazicek P, Matis P. Melatonin content in plasma and large intestine of patients with colorectal carcinoma before and after surgery. J Pineal Res 1999;27:164-9.
31. Khoory R, Stemme D. Plasma melatonin levels in patients suffering from colorectal carcinoma. J Pineal Res 1988;5:251-8.
32. Sandyk R, Awerbuch GI. Relationship of nocturnal melatonin levels to duration and course of multiple sclerosis. Int J Neurosci 1994;75:229-37.
33. Grin W, Grünberger W. A significant correlation between melatonin deficiency and endometrial cancer. Gynecol Obstet Invest 1998;45:62-5.
34. Malhotra S, Sawhney G, Pandhi P. The therapeutic potential of melatonin: A review of the science. Med Gen Med 2004;6:46.

How to cite this article: Fares A. Night-time exogenous melatonin administration may be a beneficial treatment for sleeping disorders in beta blocker patients. J Cardiovasc Dis Res 2011;2:153-5.
Source of Support: Nil, **Conflict of Interest:** None declared.