Sleep Medications Containing Melatonin can Potentially Induce Ventricular Arrhythmias in Structurally Normal Hearts: A 2-Patient Report

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Abstract: Idiopathic ventricular arrhythmias (IVAs) are relatively common in the general population and usually have a good prognosis. However, frequent premature ventricular contractions (PVCs) can lower the quality of life (in symptomatic cases) and can cause cardiomyopathy and sudden cardiac death. In this report, we demonstrate a novel trigger for IVAs. Melatonin use for treating sleep disorders has increased significantly in recent years. We provide here the first human evidence of its proarrhythmic effect by presenting 2 patients (with normal myocardium) with symptomatic PVCs, while on melatonin. Discontinuation of melatonin stopped PVCs in both patients. Our findings highlight the importance of identifying precipitating factors for IVAs.

Key Words: melatonin, ventricular arrhythmia, outflow tract

INTRODUCTION

Even in patients with a structurally normal heart, symptomatic premature ventricular contractions (PVCs) are relatively common. The majority originate in the ventricular outflow tracts (OTs). Although it is well known that triggered activity is the main underlying mechanism of arrhythmogenesis, precipitating factors for this focal activity remain largely undetected.1

Here, we report on the pineal hormone melatonin (which normally regulates the body’s circadian rhythms and sleep–wake cycles) being capable of mediating OT PVCs in the absence of structural heart disease. Melatonin is widely used as a prescription/over-the-counter drug to treat sleep disorders. Based on its pharmacological effect of alleviating sleeping problems, it is rather expected to protect against arrhythmias because of the association between arrhythmias and sleep deprivation. In our patients, however, we observed a clear association between melatonin use and the occurrence of PVCs from the OT. As OT arrhythmias represent more than 10% of overall referrals for electrophysiological studies, our present findings highlight the importance of identifying pharmacons that can mediate OT PVC generation because refraining from these drugs is safer and more cost-effective than trying to treat the disease with antiarrhythmic medication or catheter ablation.1

CASE SERIES

Two patients referred to our department because of palpitations were included in this report. Both patients used melatonin for sleeping problems. Holter and/or implantable loop recorder (ILR) registrations demonstrated PVCs as a cause for their symptoms. The origin of the PVCs was specified either through electrophysiological study or based on QRS morphology on 12-lead electrocardiogram. Patient characteristics are listed in Table 1. A comprehensive literature search in several electronic databases for relevant studies published until January 2017 was conducted. Informed consent was obtained from both patients. Data collection was performed respecting the Health Insurance Portability and Accountability Act 1996.

Case 1

The first patient was a 72-year-old man with an uneventful cardiac history (except for a short episode of paroxysmal supraventricular tachycardia in 1980). In August 2014, he was referred to our outpatient clinic because of palpitations despite being on beta-blocker therapy. Other medication used by the patient included sitagliptin (oral antihyperglycaemic), atorvastatin (statin), candesartan (angiotensin II receptor blocker), and metformin (oral antihyperglycaemic). The patient also used melatonin (1 mg once daily, sublingual) because of problems falling asleep.

Holter tracings revealed more than 2000 multif orm PVCs per 24 hours and ILR registration (Medtronic Reveal LINQ) confirmed PVCs as the cause for the palpitations. Bisoprolol (7.5 mg) was ineffective. The dominant morphology of the PVCs was suggestive of an OT origin on a 12-lead electrocardiogram (Fig. 1). An exercise test showed only occasional PVCs, both during exercise and recovery phase, and without symptoms of angina or ST segment alterations. A normal left ventricular function was seen on echocardiogram. Computed tomography angiography showed no coronary artery disease with a calcium score of zero. Subsequently, 150 mg of flecainide was given in combination with 2.5 mg of bisoprolol, but without any effect. In September and November 2014, he discontinued melatonin resulting in complete cessation of symptoms. In March 2015, after completely abstaining from melatonin, the patient became free from any symptoms.

Case 2

In May 2012, a 63-year-old man presented with recurrent palpitations after a previous cardiac history of catheter ablation of...
a left anterolateral accessory pathway, a focal atrial tachycardia and atrial fibrillation (successful catheter ablation in 2011). He also used melatonin (1 mg once daily, per os) because of difficulties falling asleep. Other medications included acetylsalicylic acid (platelet aggregation inhibitor), formoterol (long-acting β2 agonist, 12 μg 2 times daily), fluticasone, and ciclesonide (glucocorticoids).

At follow-up, in July 2012, a 5-day Holter was performed, revealing multiple symptomatic PVCs and nonsustained ventricular tachycardias (nsVTs) with a morphology suggestive of an OT origin (Fig. 1). A coronary angiogram ruled out an ischemic cause of the arrhythmia. Echocardiogram showed a normal left ventricular ejection fraction without any other structural abnormalities. In October 2012, unsuccessful PVC ablation, targeting a right ventricular outflow tract (RVOT) origin, was performed. After a 24-hour Holter revealed a PVC burden of 6% in May 2015, the patient was suggested to stop using melatonin (based on our previous experience with the patient from case 1). A follow-up 24-hour Holter registration showed a complete cessation of PVCs (0% PVC burden), and additionally, the patient became free from any symptoms.

### DISCUSSION

This is the first report in the literature that describes evidence for a possible association between melatonin use and the occurrence of idiopathic VAs in humans. Discontinuation of melatonin in 2 patients with OT VAs led to a complete suspension of symptoms and the disappearance of arrhythmias on Holter/ILR registrations.

In the absence of structural heart disease, VAs most commonly arise in the RVOT. Focal triggered activity mediated by delayed after depolarizations (DADs) is believed to account for the generation of these VAs. DADs can be evoked in the presence of various pathological factors (myocardial ischemia, genetic disorders of intracellular Ca^{2+}-handling, etc.), which can cause intracellular Ca^{2+} overload in myocytes. However, in the absence of such disorders, the mechanism of DAD-mediated arrhythmogenesis is less well understood. Increased sympathetic influence seems to play a role in the generation of DADs in normal myocardium in a cyclic adenosine monophosphate–mediated fashion.

Several “extrinsic factors” have also been implicated to cause VAs in structurally normal hearts: extensive alcohol

| TABLE 1. Patient Characteristics |
|---------------------------------|
|                                | Case 1 | Case 2       |
| Sex                             | Male   | Male         |
| Age, yr                         | 72     | 65           |
| BMI (body mass index)           | 25     | 22           |
| LVEF                            | Normal | Normal       |
| Cardiac history                 |        |              |
| Arrhythmic                      | Paroxysmal SVT | AVRT, AT, AF, AFl |
| Ischemic                        | No CAD | No CAD       |
| Melatonin dosage                | 1 mg once daily, sublingual | 1 mg once daily, per os |

AF, atrial fibrillation; AFl, atrial flutter; AT, atrial tachycardia; AVRT, atioventricular re-entry tachycardia; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; SVT, supraventricular tachycardia.

FIGURE 1. Electrocardiograms of both patients showing PVCs originating from the outflow tracts.
caffeine or tobacco use, electrolyte imbalance (hypokalemia), and certain medications represent the main examples. β-receptor activators (catecholamines and synthetic β-agonists) can cause DAD-induced VAs through the elevation of cyclic adenosine monophosphate levels and digitalis causes Ca\(^{2+}\) accumulation and subsequent DADs through the inhibition of the Na\(^+\)–K\(^+\) exchange.\(^2\)

Based on our observations, melatonin could also belong to the group of mediators that have the potential to precipitate VAs in structurally normal myocardium. In recent years, the clinical use of melatonin has increased significantly. In the United States, its use more than doubled between 2007 and 2012,\(^3\) and a similar (or even more significant) increase has been reported in Scandinavian countries.\(^4\) In Europe, the availability of melatonin as prescription versus over-the-counter drug varies from country to country. In the United States, melatonin is classified as dietary supplement and therefore available over the counter. Melatonin content of such dietary supplements is not controlled by the Food and Drug Administration (FDA), and therefore concerns may arise regarding the actual melatonin dose of these preparations.

Reports in the literature mainly argue for a protective effect of melatonin against arrhythmias. This putative antiarrhythmic effect has been implicated to occur through indirect mechanisms. As a sleep medication, it might be able to alleviate “sleep deprivation–induced arrhythmias.” In addition, by reducing the sympathetic tone, melatonin can also reduce arrhythmia burden caused by sympathetic predominance. A study that analyzed the effect of melatonin in canines on the repetitive extrasystole threshold of the vulnerable period of the ventricular myocardium showed that this threshold was increased by melatonin, thus arguing for a protective effect against arrhythmias.\(^5\) The authors proposed that this effect may be achieved by the inhibition of the flow of “arrhythmogenic” sympathetic nerve traffic from the central nervous system to the heart.\(^5\) Moreover, through its antioxidant activity melatonin has also been shown to significantly reduce ischemia/reperfusion-induced VAs.\(^6,7\)

Recent studies describe the expression of melatonin receptors in cardiac tissue.\(^8\) The 3 known melatonin receptors are MT1, MT2, and MT3.\(^9\) Of these, MT1 and MT2 have been detected in the cardiovascular system.\(^8,10\) Through these 2 G-protein–coupled receptors, melatonin might be able to alter the function of key players in the Ca\(^{2+}\)-handling machinery (eg, L-type Ca\(^{2+}\) channel, ryanodine receptor, and sarcoplasmic/endoplasmic reticulum calcium ATPase). Although a proarrhythmic mechanism has never been reported before, a presumable direct effect on the myocardium through its receptors could provide the functional basis for a proarrhythmic effect. However, (although less likely) indirect proarrhythmic effects of melatonin should also not be excluded. For instance, a seemingly paradoxical effect of melatonin is the reduction of deeper sleep.\(^11\) Through the altered sleep structure, melatonin might exert an indirect proarrhythmic effect. Another side effect of melatonin reported in literature is hypothermia,\(^11\) which in turn is thought to be a proarrhythmic condition. This proarrhythmic effect, however, is usually reported in the context of therapeutic hypothermia (between 32 and 36°C). The temperature drop associated with melatonin has been reported to be only 0.28°C after a dose of 5 mg, which therefore represents an

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**FIGURE 2.** Mean PVC number/registration period with ILR mean PVC number during registration period is depicted for each month of ILR use. All registrations were patient activated. Triangles: (re)start of melatonin, rhombuses: discontinuation of melatonin. Embedded table shows the total number and total duration of recordings during 1 month.

| Month   | Number of registrations | Duration (min) of registration |
|---------|-------------------------|-------------------------------|
| Aug-14  | 13                      | 81.5                          |
| sep-14  | 7                       | 56                            |
| okt-14  | 2                       | 16                            |
| nov-14  | 3                       | 24                            |
| feb-15  | 1                       | 8                             |
| apr-14  | 1                       | 8                             |
| jun-15  | 1                       | 8                             |
| okt-15  | 1                       | 8                             |

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unlikely mechanism for arrhythmogenesis in the patients in our current report.

The ultimate effect of melatonin (proarrhythmic vs. antiarrhythmic) might depend on the balance between its indirect versus direct effects, which in turn might be determined by several factors: eg, melatonin dosage in different preparations (especially in dietary supplements), differences in bioavailability, and genetically defined individual differences in receptor expression and receptor activity. For instance, it has been shown that there is a substantial person-to-person variability in bioavailability (with up to 25-fold variations in areas under the curve of a single dose in 5 subjects in 1 study).12 Time to maximum melatonin levels and half-life elimination may range between 40 and 90 minutes and 50–120 minutes, respectively.13,14 Hence, our patients might represent a certain population, the members of which might either show greater susceptibility to the proarrhythmic effects of melatonin or possess an altered pharmacokinetics and different bioavailability of this drug. Both of these conditions could lead to the development of symptomatic VAs in response to this medication.

When taking into consideration other possible triggers of PVCs, it is noteworthy to mention that the patient from case 2 used formoterol, which is known to have the potential of symptomatic VAs in response to this medication. As native English speaker, R. Alloway revised the manuscript for language.

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