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LETTER TO THE EDITORS

Ivabradine and nightmares: a previously unreported adverse reaction

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Dear Sirs:

Ivabradine, an inhibitor of the *If* current in the sinoatrial node, has been proven to be of benefit in coronary heart disease and heart failure. Frequent adverse reactions include bradycardia and visual disturbances due to local, peripheral effects. Central nervous symptoms have generally not been expected because of poor penetration of the blood–brain barrier [1]. We report a case where use of ivabradine was associated with nightmares. The effects of discontinuation and re-exposure strongly indicate a causal relationship.

The patient was a 25-year old woman with a 5-year history of tachycardia. Resting heart rate was >100 bpm and she had limited work and exercise capacity due to an unphysiological heart rate response. Her sleep was poor and often interrupted by palpitations, but she had never been troubled with nightmares. Inappropriate sinus tachycardia was diagnosed; metoprolol was tried, but had to be discontinued because of adverse reactions, including fatigue and cold extremities. She used no over-the-counter drugs or any other supplements. Ivabradine (5 mg bid) was started and resulted in an immediate improvement in heart rate and symptoms. However, within a few days she experienced nightmares occurring several nights every week. Nevertheless, her general well-being improved to the extent that she chose to continue with the drug. After about 4 weeks on ivabradine, pregnancy was discovered and she immediately discontinued the drug. No other drugs were used. The nightmares disappeared without any delay. Some weeks later the pregnancy was terminated, ivabradine was re-started and the nightmares returned within a few days. Again, the improvement in general wellbeing on ivabradine out-weighed the negative effects and she chose to continue taking the drug without any change in frequency or intensity of the nightmares.

Ivabradine acts by inhibiting the *If* current in the sinoatrial node. The *If* current is carried by hyperpolarization-activated, cyclic nucleotide-gated cation (HCN) channels [2]. Two large clinical trials demonstrate benefit in subgroups of patients with coronary artery disease and heart failure [3–5]. Case reports and case series show a possible beneficial effect in inappropriate sinus tachycardia [6–10] and postural orthostatic tachycardia syndrome [11]. Common adverse reactions reported in clinical trials include bradycardia, visual disturbances (including light sensitivity), headache and dizziness [1, 12]. Ivabradine was licensed for the treatment of stable angina pectoris by the European Medicines Agency (EMA) in 2005 [13].

To our knowledge, nightmares have not been previously associated with ivabradine. The reaction is presumably mediated by effects in the central nervous system. A number of pharmacological agents (both psychotropic and nonpsychotropic), displaying a wide range of pharmacological mechanisms, are reported to induce nightmares. Many of these agents exert effects on neurotransmitters like serotonin and dopamine, and beta-blockers affecting norepinephrine neuroreceptors are among the drugs most frequently reported to induce nightmares [14].

In addition to sinus node inhibition, ivabradine also inhibits HCN channels carrying the *Ih* current in the eye

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and CNS neurons. The visual disturbances observed during therapy with ivabradine are thought to be caused by inhibition of the *Ih* current in the retina [1, 2]. Substantial inhibition of the *Ih* current in CNS neurons and associated symptoms contributed to withdrawal from further development of several first-generation specific bradycardia agents, such as alinidine, falipamil, and ZD-7288 [1]. Ivabradine is hydrophilic, and low distribution to the brain is demonstrated in animal studies. Following a single dose the level of ivabradine in the brain represented at most 3% of the plasma exposure in rats [12]. It is therefore generally claimed that ivabradine does not cross the blood–brain barrier, and is hence not suspected of having any effect on the *Ih* current in central nervous neurons [1, 2, 12, 13]. Central nervous symptoms have not been reported to be of concern in clinical trials with ivabradine; however, in one of the major trials the frequency of serious psychiatric adverse reactions was 0.3% with ivabradine versus 0.1 % with placebo [3]. Concerning the low lipid solubility of ivabradine it should also be mentioned that several cases of nightmares have been reported during therapy with the highly hydrophilic beta-blocker atenolol [14, 15]. To our knowledge it is not known whether inhibition of the *Ih* current in the CNS neurons can induce nightmares, and the mechanism behind ivabradine-associated nightmares is thus unknown.

Ivabradine is a relatively new drug, with limited knowledge about rare adverse reactions. These are often detected only after the medicine has been used by a larger and unselected group of patients. In the present case the nightmares disappeared when the patient stopped taking ivabradine and reappeared after re-introduction of the drug. The Naranjo probability scale consists of ten questions related to drug exposure and adverse events, where the answers are converted to numbers. When applied to our patient, the scale indicates a probable relationship (with a value of 7) between the nightmares and the use of ivabradine [16]. Our case thus implies that ivabradine can cross the human blood–brain barrier in amounts sufficient to exert pharmacological effects. Adverse reactions like nightmares, and possibly also other central nervous symptoms, should therefore not be ruled out during therapy with ivabradine.

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Conflicts of interest The authors declare that they have no conflict of interest.

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