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Case Report

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Resolution of Sinus Tachycardia Secondary to Hyperthyroidism With Ivabradine

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Abstract

Currently, ivabradine is not approved for the treatment of sinus tachycardia secondary to hyperthyroidism. We aimed to increase the recognition of ivabradine as an effective alternative to, or combination with, beta-blockers in controlling sinus tachycardia secondary to hyperthyroidism. Elevated thyroid hormone levels enhance cardiac performance through a positive chronotropic effect, resulting in an increased heart rate (HR), an effect brought on by increasing the I_f funny current at sinoatrial node (SAN). Ivabradine is a novel, dose-dependent selective inhibitor of I_f channels. By decreasing SAN pacemaker activity, ivabradine allows for selective reduction of HR with a resultant increase in ventricular filling time. This mechanism sets ivabradine apart from the typical rate-reducing medications, namely beta-blockers and calcium channel blockers, which simultaneously decrease HR and myocardial contractility. We describe a case of hyperthyroidism-induced sinus tachycardia, resistant to maximal doses of beta-blocker, which was successfully managed by ivabradine. After excluding other causes of tachycardia, such as anemia, hypovolemic states, structural heart disease, drug abuse, and infection, ivabradine was given off-label for symptomatic relief of hyperthyroidism-induced sinus tachycardia. Within 24 h, HR steadily decreased to the low 80s. Our patient had a unique presentation in which he presented with hyperthyroidism-induced sinus tachycardia with no relief after administration of maximal dose of beta-blocker. Ivabradine was then given, with resolution of sinus tachycardia within 24 h.

Keywords: Electrophysiology; Tachycardia; Tachyarrhythmia; Hyperthyroidism

Introduction

Sinus tachycardia is a classic rhythm disturbance found in patients with hyperthyroidism, a condition resulting from excessive production of thyroid hormone (TH) [1, 2]. TH exerts a positive chronotropic effect on the heart by genomic and cellular mechanisms, subsequently leading to an increased heart rate (HR) [3]. One of the proposed mechanisms by which TH, specifically, triiodothyronine (T3) is thought to impact sinoatrial node (SAN) activity directly is by increasing the I_f pacemaker current, a critical determinant of spontaneous SAN firing and therefore, rate modulation [4]. T3 has also been suggested to enhance the expression of I_f channels in SAN myocytes [5, 6]. First-line therapy traditionally consists of initial symptomatic relief with beta-blockers, followed by anti-thyroid medications or radioactive iodine ablation to treat the underlying disease. However, beta-blockers may have undesirable side effects or be contraindicated in specific patient populations, prompting the need to investigate alternative therapy options.

Ivabradine, a novel selective inhibitor of I_f channels, is increasingly being studied for its role in the treatment of sinus tachycardia of varying origins [7] and is frequently well tolerated. Ivabradine is unique in that it causes dose-dependent selective inhibition of I_f channels, thereby decreasing SAN pacemaker activity, allowing for selective reduction of HR with a resultant increase in ventricular filling time and without significant effects on contractility [8, 9]. This mechanism sets ivabradine apart from the typical rate-reducing medications, namely beta-blockers and calcium channel blockers, which simultaneously decrease HR and myocardial contractility. Ivabradine was first approved for use in 2005 by the European Medicines Agency (EMA) for stable angina with normal sinus rhythm (NSR) refractory to beta-blocker therapy [7]. It has only been approved in the USA since 2015 and is currently solely indicated for stable patients with systolic heart failure (HF) and HR of 70 beats per minute (bpm) on maximally tolerated beta-blocker therapy or in cases in which beta-blocker use is contraindicated. A case series of 20 patients by Ptaszynski et al revealed that while metoprolol succinate and ivabradine resulted in similar decreases in HR, ivabradine appeared to be more successful in ameliorating symptoms brought on by physical activity [10]. This study highlighted the potential use of ivabradine as second-line therapy in conjunction with maximally tolerated beta-blocker therapy or as a stand-alone treatment when beta-blockers are contraindicated or ineffective.

Given the proposed role of T3 in I_f current regulation, the selective I_f channel inhibitor ivabradine may have a potential role in treating sinus tachycardia in the setting of hyperthyroidism. Here, we describe a case of persistent sinus

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tachycardia secondary to undiagnosed severe hyperthyroidism refractory to maximal doses of propranolol. Subsequent addition of off-label ivabradine to beta-blocker therapy resulted in the resolution of tachycardia and associated symptoms. To our knowledge, this is the first reported use of ivabradine in hyperthyroidism-related tachycardia in the USA.

Case Report

Investigations

Our patient is an 81-year-old male who presented to our emergency room (ER) with new-onset worsening shortness of breath on exertion of 2 weeks duration associated with intermittent palpitations, excessive sweating, and loose bowel movements, with no previous history of such symptoms. His symptoms improved with rest with no other alleviating factors. He usually slept on one pillow and does not experience shortness of breath while lying flat. He denied any chest pain, dizziness, orthopnea, or lower extremity edema. His medical history was significant for interstitial lung disease (ILD), coronary artery disease (CAD) status post coronary artery bypass graft surgery, heart failure with reduced ejection fraction (HFrEF) status post cardiac resynchronization defibrillator (CRT-D), and hypertension. A cardiac electrophysiologist evaluated his CRT-D, which was determined to be working properly with no events in dual chamber pacing (DDD) mode with a rate of 80 bpm. His current medications include aspirin, clopidogrel, metoprolol, losartan, and spironolactone, which he is compliant with. The patient had previously worked in an electronics factory and admitted to frequent exposure to chemical fumes during his employment. He is a former smoker and quit 40 years ago.

Upon presentation to the ER, the patient appeared to be in mild distress with moist hands with an average supine blood pressure of 106/63 mm Hg. Resting HR ranged from 110 - 120 bpm, temperature 37.1 °C and saturating of 96% on room air. The patient was placed on telemetry monitoring, which showed his HR reaching a maximum of 150 bpm. Physical examination was significant for bilateral fine basilar crackles. No thyroid enlargement, lower extremity edema, or jugular venous distension was appreciated.

Diagnosis

Laboratory analysis was significant for a low thyroid-stimulating hormone (TSH) of 0.02 mU/L (normal range 0.4 - 4.0 mU/L), elevated brain natriuretic peptide (BNP) of 867 pg/mL, and hemoglobin A1c (HbA1c) of 5.8%. Echocardiogram showed a left ventricular ejection fraction of 20-25% with grade III diastolic dysfunction. Electrocardiogram (EKG) showed an atrial sensed ventricular paced rhythm. Pacemaker-mediated tachycardia was ruled out. Echocardiogram showed a left ventricular ejection fraction of 20-25% with grade III diastolic dysfunction. A chest computed tomography (CT) with intravenous (IV) contrast showed no evidence of pulmonary edema or effusions or acute central or lobar pulmonary embolism. Hyperthyroidism was confirmed by the patient's low TSH of 0.02 mU/L with free thyroxine (FT4) level of 82.3 pmol/L (normal range 12 - 22.0 pmol/L) and ultrasound of the thyroid showing homogenous echogenicity with normal thyroid size along with associated symptoms such as excessive sweating.

Treatment

After consulting with the endocrinology team, the patient was started on propranolol for symptomatic relief and methimazole 20 mg every 8 h to treat the underlying severe hyperthyroidism. Despite receiving maximally tolerated doses of propranolol of 60 mg every 8 h, the patient continued to experience symptomatic palpitations with sinus tachycardia. After excluding other underlying or exacerbating causes for his tachycardia, such as anemia, hypovolemic states, structural heart disease, drug abuse, and infection, the patient was started on ivabradine after discussion with the cardiac electrophysiologist. In this instance, ivabradine was given for the off-label indication of symptomatic relief of hyperthyroidism-induced sinus tachycardia, during which methimazole had been started but has yet to take full effect, with typical onset of action about 1 - 4 weeks. Within 24 h, HR steadily decreased to the low 80s. Over the next 48 h, his shortness of breath subjectively improved. The patient was also closely monitored for atrial fibrillation, a potential side effect of ivabradine.

Follow-up and outcomes

At discharge, his HR was 81 bpm, blood pressure was 110/60 mm Hg, and oxygen saturation was 95% on room air. He was prescribed a 2-week course of ivabradine 5 mg every 12 h in addition to propranolol and methimazole in addition to his HF medications. After 2 weeks, follow-up visit showed HR averaged at 80 bpm, and he remained symptom free.

Discussion

To date, this is the first reported case of severe hyperthyroidism-induced sinus tachycardia resistant to maximal doses of propranolol that was successfully managed by ivabradine in the USA. Ivabradine is a novel drug that selectively inhibits I_f "funny" channels in a dose-dependent manner, decreasing SAN activity, allowing for a selective reduction of HR without any appreciable effect on contractility, thus enabling an increase in ventricular filling time. This mechanism underlies the usefulness of ivabradine in decreasing HR in patients with HFrEF. Our successful use of ivabradine as an adjunctive treatment to propranolol for hyperthyroidism-induced tachycardia not only highlights the proposed effects of TH on I_f channels but also shows that ivabradine has significant promise to be approved for this purpose in the future.

One study using rat models had previously reported that

HR reduction achieved with ivabradine decreased the extent of TH-induced cardiac remodeling, suggesting that ivabradine may be useful not only for symptomatic relief of symptomatic sinus tachycardia in patients with hyperthyroidism, but also in reducing the risk of tachycardia-induced cardiomyopathy, a potential complication of chronic sinus tachycardia. Recently, a case report from UK detailed the successful use of ivabradine, combined with carbimazole in the treatment of a patient with thyrotoxic cardiomyopathy and associated tachycardia. Large, prospective studies and randomized trials investigating both a combination of ivabradine and beta-blockers and ivabradine alone will be needed in the future to determine the extent to which ivabradine is effective in this setting.

Learning points

Interestingly, our patient had a separate indication for ivabradine, as he exhibited a HR greater than 70 bpm and had a history of HFrEF and CAD while on maximally tolerated beta-blocker therapy. The administration of ivabradine may have the additional benefit in our patient of improving cardiovascular morbidity and mortality, as ivabradine, in conjunction with beta-blocker therapy, has been shown to decrease the risk of major cardiovascular events through reducing HR in the setting of CAD and HF [11]. At this time, ivabradine is not approved for the treatment of sinus tachycardia secondary to hyperthyroidism. However, our case demonstrates the benefit of ivabradine has been promising, emphasizing the novelty of this case. In cases of hyperthyroidism-induced sinus tachycardia, in the acute setting, ivabradine can be considered when beta-blockers fail to improve the heart rate. Nonetheless, caution should be taken given potential side effects like atrial fibrillation. We hope our article will help push ivabradine into the spotlight as an effective alternative or in combination with beta-blockers in controlling sinus tachycardia secondary to hyperthyroidism.

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Conflict of Interest

None to declare.

Informed Consent

Authors confirm that informed consent was obtained.

Author Contributions

Study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation: Y. Medina, A. Khan, J. Spagnola, and J. Lafferty. All authors reviewed the results and approved the final version of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

HR: heart rate; SAN: sinoatrial node; TH: thyroid hormone; T_3: triiodothyronine; EMA: European Medicines Agency; NSR: normal sinus rhythm; bpm: beats per minute; ILD: interstitial lung disease; CAD: coronary artery disease; HFrEF: heart failure with reduced ejection fraction; CRT-D: cardiac resynchronization defibrillator; TSH: thyroid-stimulating hormone; FT4: free thyroxine

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