CLINICAL VIGNETTE

Central Sleep Apnea Caused by Ticagrelor

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Case

A 60-year old male presented to the emergency room with acute shortness of breath and air hunger upon falling asleep. He was unable to sleep at all due to these symptoms. He had a history of obstructive coronary disease, with coronary stenting two days prior to the onset of dyspnea. The patient's past medical history also includes hypertension, hyperlipidemia and obesity. Notably, the patient had no prior history of obstructive sleep apnea. Past surgical history was significant for LapBand surgery for weight loss. His medications were: atenolol 100 mg daily, losartan 100 mg daily, evolocumab 140 mg SQ every 2 weeks, Aspirin 325 mg daily, ticagrelor 60 mg twice a day. He was allergic to sulfa, but had no other allergies to medications. The emergency room physician noticed that the patient would become apneic as soon as he would fall asleep. On arrival to the emergency room, the patient was normotensive, with normal heart rate and oxygen saturation on room air. His electrocardiogram was normal. His chest radiograph was normal. A transthoracic echocardiogram revealed normal left ventricular size, borderline concentric left ventricular hypertrophy, normal systolic function with a small distal left anterior descending territory regional wall motion abnormality, and normal left ventricular diastolic function. Left ventricular ejection fraction was approximately 60 to 65% and there was normal right ventricular size and normal systolic function. Mild aortic valve sclerosis without stenosis was reported, with normal estimated mean pulmonary artery pressure. A trivial sized posterior pericardial effusion was noticed. A prior echocardiogram was reviewed for comparison, and the regional wall motion abnormality was new compared to the prior study.

The patient's lab tests included normal complete blood count, comprehensive metabolic panel, prothrombin time and partial thromboplastin time. His troponin level was 0.16 ng/mL, followed by serial troponin levels of 0.24 and 0.26 ng/mL (normal range <0.04 ng/mL). His B-type natriuretic peptide (BNP) was 119 pg/mL (normal range <100 pg/mL). The emergency room physician suspected an acute coronary syndrome, possibly related to stent thrombosis and the patient received an additional dose of Aspirin and Ticagrelor. A cardiology consult was requested.

The cardiologist suggested that the patient's mild troponin elevation and small distal left anterior descending territory wall motion abnormality was expected after stenting. He attributed the apneic episodes and dyspnea to ticagrelor, and recommended that the patient be admitted for observation, as he had received an additional dose of ticagrelor in the emergency room, to treat presumptive stent thrombosis. The cardiologist also recommended initiation of clopidogrel treatment to replace ticagrelor. The patient's condition subsequently improved and he was discharged home without further apneic episodes.

Discussion

Ticagrelor is a $P2Y_{12}$ receptor antagonist used in first-line dual-antiplatelet therapy in coronary artery disease. One of the reported side effects of ticagrelor is dyspnea, but there are only rare reports of central sleep apnea related to this medication.

Gianonnoni et al reported Cheyne-Stokes respiration with central sleep apnea in 4 patients after ticagrelor therapy was initiated, which disappeared after ticagrelor withdrawal and switch to clopidogrel.[1]

Revol et al analyzed reports of sleep apnea and dyspnea among ticagrelor users, and compared the use of ticagrelor to the use of other antiplatelet agents by performing an analysis of VigiBase, the World Health Organization Global Individual Case Safety Reports (ICSRs) database, including >16 million ICSRs collected from 127 countries.[2] Among the 13,636 ADRs (adverse drug reactions) reported with ticagrelor therapy, there were 28 cases of sleep apnea, and 2,665 cases of dyspnea. In 9 of the 28 cases, sleep apnea and dyspnea were simultaneously reported. OR (odds ratio) values for ticagrelor were significant for sleep apnea (OR: 4.16; 95% CI: 2.87 to 6.03) and for dyspnea (OR: 8.26; 95% CI: 7.92 to 8.62). This was not the case for other antiplatelet agents, like clopidogrel (OR: 0.55; 95% CI: 0.33 to 0.93; 14 apnea cases; and OR: 0.67; 95% CI: 0.63 to 0.71; 988 dyspnea cases); prasugrel (OR: 1.08; 95% CI: 0.41 to 2.89; 4 apnea cases; and OR: 1.12; 95% CI: 0.99 to 1.28; 239 dyspnea cases); or aspirin (OR: 0.57; 95% CI: 0.41 to 0.80; 35 apnea cases; and OR: 0.96; 95% CI: 0.92 to 0.99; 3,374 dyspnea cases).

Ticagrelor may cause sleep apnea as a consequence of its antagonism of microglial $P2Y_{12}$ receptors.[1] However, ticagrelor is not known to cross the blood–brain barrier, and there is no known impact of clopidogrel or prasugrel on the incidence of sleep apnea, despite the potential for active metabolites of these drugs to also block microglial $P2Y_{12}$ receptors. The effects of ticagrelor on pulmonary C fibers may be a more likely mechanism for Cheyne-Stokes respiration, either as a consequence of

ticagrelor's inhibition of the type 1 equilibrative nucleoside transporter (ENT1) protein and its effects on tissue adenosine levels, or due to the putative $P2Y_{12}$ receptors on the pulmonary C-fibers.[3]

Giannoni et al[1] described a patient with dyspnea on ticagrelor in whom 24-hour respiratory monitoring revealed the presence of Cheyne–Stokes respiration (central apnea and hyperpnea), which occurred both at night and during the day. The rebreathing technique (breathing circuit in which exhaled air is inhaled with or without absorption of carbon dioxide or oxygen) showed increased chemosensitivity to hypercapnia, and normal chemosensitivity to hypoxia.

Lamberts et al[4] described a patient with dyspnea and Cheyne–Stokes respiration, which was difficult to suppress. Polysomnography (PSG) confirmed the existence of Cheyne-Stokes respiration, with an apnea-hypopnea index (AHI) of 31.7/h of sleep.

Meurin et al[5] conducted a prospective study of 121 patients after acute coronary syndrome (ACS), with no heart failure (left ventricular ejection fraction $\geq$ 45%) and no sleep apnea identified during a supervised sleep study. In total, 49 (45.3%) patients had AHI (apnea-hypopnea index) $\geq$ 15, 27 (22.3%) patients had CSAHS (central sleep apnea/hypopnea syndrome), and 22 (18.2%) patients had OSAHS (obstructive sleep apnea/hypopnea syndrome). For 80 patients receiving ticagrelor, 24 (30%) had CSAHS with AHI $\geq$ 15, and for 41 patients not taking ticagrelor, only 3 (7.3%) had CSAHS with AHI $\geq$ 15 (chi-square = 8, p = 0.004). On multivariable analysis, only age and ticagrelor administration were associated with the occurrence of CSAHS, (p = 0.0007 and p = 0.0006).

After initiation of ticagrelor treatment, it is important for medical providers and patients to be aware of the potential side effect of central sleep apnea, which can cause dyspnea that can be erroneously attributed to an acute coronary event. In such cases, it is important to promptly discontinue ticagrelor and initiate an alternative treatment like clopidogrel, which is less likely to cause similar side effects.

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