MAYO CLINIC

Coronary Vasospasm Induced by Phentermine

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Coronary artery spasm is a complex clinical entity characterized by sudden, reversible vasoconstriction of a coronary artery causing subtotal or total occlusion and compromise of myocardial blood flow. First described by Prinzmetal et al in 1959 as a cause of nonexertional angina, coronary vasospasm is now known to cause an array of myocardial ischemic syndromes, from angina to fatal acute myocardial infarction.[1] In recent years, it has been labelled the "forgotten coronary disorder"; however, routine provocative testing reveals an incidence of approximately 30% in patients presenting with myocardial infarction with no obstructed coronary arteries. In patients with typical vasospastic angina symptoms or myocardial infarction with no evidence of obstructive disease, clinician vigilance and a low threshold for considering coronary artery vasospasm are essential, as treatment differs significantly from traditional atherosclerotic therapies. Moreover, an extensive and thorough review of pharmacologic therapies and recreational drugs must not be forgotten, as continuation of a causal agent may prove fatal.

Although not fully understood, it appears that increased hyperreactivity of coronary vascular smooth muscle is central to the pathophysiology of coronary vasospasm. Smooth muscle cell hyperreactivity is largely a result of increased calcium sensitivity rather than increased calcium concentration.[2] Typically, following smooth muscle cell contraction, myosin light chain phosphatase dephosphorylates myosin, leading to smooth muscle cell relaxation. In patients with coronary vasospasm, Rho kinase, an enzyme that inhibits this process, is believed to play an important role in smooth muscle hyperreactivity.[3] Inflammation, endothelial dysfunction, and autonomic modulation have also been implicated in its pathogenesis. Clinically, a combination of predisposing factors and precipitating stressors appear to contribute to an acute event of coronary vasospasm. Of the traditional cardiovascular risk factors, only smoking has been associated with an increased risk; however, age between 40 and 70 years and high C-reactive protein levels may also predispose to the condition.[3] Additionally, either sympathetic or parasympathetic modulation often precedes spontaneous spasm attacks. Although largely based on case reports and small case series, known triggers for this include illicit drug use, sympathomimetic agents, and altered autonomic activity before or during sleep.

In this issue of *Mayo Clinic Proceedings*, Prasad et al describe two interesting cases of coronary vasospasm associated with the weight loss drug phentermine in middle-aged women who were also smokers and had underlying coronary atherosclerosis.[4] In both instances the patients experienced recurrent episodes of chest pain commencing shortly after taking the drug, before eventually presenting with acute coronary syndromes. Diagnosis was made by invasive coronary angiography after stenotic lesions were observed to resolve with intracoronary nitroglycerin. Both histories suggest that commencement of phentermine was the precipitating stressor for coronary spasm and underline the diagnostic dilemmas of this condition that require a high index of suspicion and astute clinical acumen.

From 2008 to 2011, 25.3 million scripts of phentermine were issued in the United States, primarily for short-term weight loss.[2] Phentermine is an amphetamine analogue, acting to enhance activity of the sympathetic nervous system, primarily modulating norepinephrine, but also serotonin and dopamine release in

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the autonomic nervous system. All three of these autonomic neuromodulators have been implicated as precipitating factors or pathophysiologic mediators in coronary vasospasm.[1] Furthermore, many case reports of illicit cocaine and amphetamine use (both of which also cause increased norepinephrine) resulting in myocardial infarction have been attributed to epicardial coronary artery spasm.[5] Previously, only four other cases of coronary spasm related to phentermine have been documented, all of which occurred in patients between the ages of 24 and 41 years.[6-8] The two cases of phentermine-related spasm reported in this issue of *Mayo Clinic Proceedings* occurred in slightly older women, aged 47 and 48 years, respectively.

Intentional weight loss is an important preventative measure for cardiovascular disease; reductions in weight often concurrently improve biochemical markers and reduce or even reverse progression of atherosclerotic disease, reducing the risk of atherosclerosis-related angina or myocardial infarction.[9] Recently, the US Food and Drug Administration has approved low-dose phentermine for long-term use in weight loss. Although phentermine has been used for short-term weight loss for more than a century, very few safety trials have lasted longer than 6 months, and current long-term safety profiles are based on the combination therapy phentermine/topiramate. Dosage of phentermine in combination therapy is similar to low-dose monotherapy. Phentermine/topiramate was the first drug approved for long-term management of obesity. Recently, four large clinical trials, Evaluation of Phentermine and Topiramate Versus Phentermine/Topiramate Extended-Release in Obese Adults (EQUATE), Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP), Effects of Low-Dose, Controlled-Release, Phentermine Plus Topiramate Combination on Weight and Associated Comorbidities in Overweight and Obese Adults (CONQUER), and Two-Year Sustained Weight Loss and Metabolic Benefits with Controlled-Release Phentermine/Topiramate in Obese and Overweight Adults (SEQUEL), have studied the efficacy and safety of phentermine/topiramate in 5186 patients over a follow-up of 28 to 108 weeks.[10] No major adverse cardiac events were reported in the treatment group in any of these studies. Although current evidence therefore suggests that phentermine is safe and that combination therapy may even reduce the risk of cardiovascular events in obese patients, the incidence of coronary vasospasm, particularly in individuals with a history of smoking or underlying atherosclerosis, has not been characterized. As a result, clinicians and patients should be vigilant, educated, and aware of this rare, life-threatening complication, particularly in those with significant past or current smoking history. In patients with myocardial infarction with no clear obstructive cause, a high index of suspicion for coronary vasospasm is essential. Moreover, clinicians must perform a rigorous and thorough drug history, both prescription and recreational, to identify possible causative agents and advise their cessation to prevent possibly fatal consequences of recurrent events.

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