

Switching from Nitrate Therapy to Ranolazine in Patients with Coronary Artery Disease Receiving Phosphodiesterase Type-5 Inhibitors for Erectile Dysfunction

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ABSTRACT: Coronary artery disease (CAD) and erectile dysfunction (ED) frequently coexist. The introduction of phosphodiesterase type-5 (PDE-5) inhibitors has revolutionized medical management of organic ED; however, in patients with angina pectoris, a common symptom of CAD, coadministration of PDE-5 inhibitors and nitrates has been implicated in CAD-related deaths following sexual activity. The mechanism of action of PDE-5 inhibitors results in a potential cumulative drop in blood pressure (BP); thus, these agents are contraindicated in patients receiving nitrates. Beta-blockers and calcium channel antagonists are considered the mainstays of antianginal therapy, but may not be tolerated by all patients. Ranolazine is an antianginal agent that produces minimal reductions in heart rate and BP. Here we report three cases of men with CAD, chronic angina, and concomitant ED. We describe our treatment approach in these patients, using ranolazine as a potential substitute to nitrate therapy.

KEYWORDS: myocardial ischemia, arteriosclerosis, erectile dysfunction, phosphodiesterase type-5 inhibitors

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Introduction

Data from the National Health and Nutrition Examination Survey from 2007 to 2010 suggest that 15.4 million American adults aged ≥ 20 years suffer from coronary artery disease (CAD). Angina pectoris is a common symptom of CAD that affects ~ 7.8 million people in the United States (US), with 18% of coronary attacks preceded by long-standing angina pectoris.¹

Common antianginal agents include beta-adrenergic receptor blockers, calcium channel antagonists, and short- and long-acting nitrates. Beta blocking agents and calcium channel antagonists have several side effects, such as reducing heart rate, myocardial contractility, and blood pressure (BP), and may not be well tolerated by all patients.^{2,3} In addition, chronic nitrate use may result in tachyphylaxis or nitrate tolerance.^{3,4}

Attempts can be made to avoid or minimize the development of tolerance by altering the dose and administration schedule of the nitrate to include a nitrate-free interval; however, that can lead to periods of time where patients have subtherapeutic antianginal protection.⁵

An estimated 18% of the male population in the US aged >20 years suffers from erectile dysfunction (ED), with a total estimate of 18 million men affected by ED.⁶ ED in men can have a significant effect on psychological and physiologic well-being and quality of life, and can impair interpersonal and marital relationships.^{7,8} The degree of ED-related functional impairment can be assessed by the abbreviated International Index of Erectile Function-5 (IIEF-5) questionnaire. The IIEF-5 consists of five questions with each item scored on a 5-point ordinal scale, where lower values represent



poorer sexual function. The IIEF-5 score ranges from 5 to 25 and classifies ED into five categories: severe (5–7), moderate (8–11), mild to moderate (12–16), mild (17–21), and no ED (22–25).^{9,10} Notably, CAD and ED frequently coexist,^{11,12} with increased ED prevalence rates between 49% and 75% reported in patients with CAD.¹² Since the introduction of the phosphodiesterase type-5 (PDE-5) inhibitor sildenafil in 1998, oral therapy with PDE-5 inhibitors has revolutionized medical management of organic ED, defining ED as mainly a vascular (rather than psychogenic) condition in a majority of cases. Presently, four PDE-5 inhibitors (sildenafil, vardenafil, tadalafil, and avanafil) are FDA approved in the US for the management of ED, and these agents are widely used to treat patients with ED.^{13,14}

Therapy with PDE-5 inhibitors is generally considered safe; however, coadministration of PDE-5 inhibitors and nitrates has been implicated in CAD-related deaths following sexual activity.¹⁵ PDE-5 inhibitors promote blood flow to the penis and improve erectile function by reducing degradation of cyclic guanosine monophosphate (cGMP), while organic nitrates are nitric oxide donors, stimulating the production of cGMP through the release of guanylyl cyclase.¹⁶ The subsequent overproduction of cGMP and the potential of a cumulative drop in BP is the basis for the absolute contraindication of concomitant use of PDE-5 inhibitors in patients receiving nitrates. Similarly, nitrates should not be administered in patients with chronic angina without exclusion of PDE-5 inhibitor use. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend that nitrates should not be administered within 24–48 hours of PDE-5 inhibitor administration in patients with CAD.¹⁷

In this series, we report three cases of men with CAD and chronic angina, and concomitant ED.

Case 1

A male in his 50s had a well-documented history of CAD diagnosed in 2005 after a non-ST-segment elevation myocardial infarction that did not require revascularization. He had diffuse mild coronary atherosclerosis with absence of high-degree coronary artery stenosis, which was determined by coronary angiography at the time of CAD diagnosis. In addition, a recent stress test performed in the same year did not reveal any objective signs of stress-induced myocardial ischemia. He was treated with oral metoprolol 25 mg twice daily, atorvastatin 40 mg once daily, low-dose (81 mg) aspirin, and isosorbide dinitrate 20 mg once daily, as well as additional sublingual nitroglycerin 0.4 mg as needed for chest pain. The doses of beta-blockers and nitrates were titrated to the patient's ability to tolerate the treatment. Coronary vasospasm is part of the differential diagnosis but cannot be completely ruled out in any patient. Adding or switching to a calcium channel blocker is a theoretical treatment option but was not done at the time we managed this patient's case because prior attempts at

increasing the dosages of beta-blockers and nitrates or adding calcium channel blockers produced dizziness, likely the result of hypotension.

During a routine clinic visit, the patient was symptomatic and reported three to four episodes of angina with exertion per week. The angina had been unchanged for several years, and was accepted and tolerated by the patient. In addition, the patient also appeared depressed. After further evaluation, we discovered that the patient had developed ED within the last year that had created significant marital and psychological problems. We subsequently administered the abbreviated IIEF-5 questionnaire for ED assessment.¹⁰ The patient scored 8, indicating moderate ED; as a result, it was suggested to the patient that his preexisting nitrate medications be discontinued to facilitate prescription of a PDE-5 inhibitor for his organic ED.

The contraindication and potential risks of concomitant nitrate and PDE-5 inhibitor use were explained. Initially reluctant to discontinue nitrate therapy for fear of an angina occurrence during sexual intercourse, the patient ultimately agreed to discontinue nitrates and initiation of a 3-week test course of ranolazine at 500 mg twice daily, prior to permanently discontinuing nitrates and beginning therapy with tadalafil for his ED. In accordance with standard procedures at our institution, he was advised to go to the nearest emergency room if he experienced any episodes of intractable chest pain after discontinuing nitrates. In addition, as is our practice, he was advised to abstain from nitrate use while being treated with tadalafil.

During the 3-week period, the patient did not report experiencing an angina attack with exertion, in contrast to his previous reports of three to four episodes of angina upon exertion per week before receiving ranolazine therapy. Tadalafil, as well as oral nitric oxide (Neo40™) supplementation, was subsequently administered, and the IIEF-5 was repeated after 2 months. The patient scored 19, which represented a significant improvement in satisfaction with his sexual function compared with his score before receiving tadalafil for his ED. No severe side effects were reported during this time period or during additional follow-up while the patient remained on ranolazine therapy.

Case 2

During an outpatient clinic visit, a male in his 70s with a history of CAD and type 2 diabetes mellitus appeared hemodynamically stable and was receiving treatment with digoxin 0.125 mg daily, atenolol 50 mg daily, hydrochlorothiazide (HCTZ) 25 mg daily, metformin 500 mg twice daily, captopril 25 mg daily, and simvastatin 20 mg daily. The patient described having dyspnea with exertion, and his left ventricular ejection fraction measured 45–50% by two-dimensional transthoracic echocardiography. The patient had a history of coronary artery bypass grafting 5 years earlier. Coronary angiography less than 6 months prior to this



presentation showed open grafts but diffuse coronary sclerosis distal to the coronary anastomosis in the distal left anterior descending without any interventional or surgical treatment options. His symptoms were regarded as an angina equivalent and categorized according to the Canadian Cardiovascular Society (CCS) classification as CCS classes II–III. The patient also complained about problems maintaining an erection. He had taken sildenafil prescribed by his primary care physician with some improvements in his sexual performance.

In order to adequately treat his angina equivalent and improve his ED problems, the following medication adjustments were made: (1) HCTZ was discontinued (because of its known effects on sexual function), and he switched to furosemide; (2) digoxin was discontinued because it was felt that the patient did not have any indication to be on digoxin at this point; (3) atenolol was discontinued and exchanged with carvedilol; and (4) captopril was discontinued and exchanged with valsartan. These changes were based on case reports from several publications and our clinical experience.^{18–20}

The patient stated that he wanted to continue using sildenafil. For his angina-equivalent symptoms with moderate exertion (such as sexual intercourse), he was prescribed oral ranolazine 500 mg twice daily that was further increased to 1000 mg orally twice daily after 1 month.

At 3 months follow-up, the patient did not report any anginal symptoms, and his erectile function was improved after taking sildenafil. The percentage of successful sexual attempts increased from 10% before the above medication to 35% after therapy, and his CCS class improved from III to 0–I.

Case 3

A male patient in his 40s with symptomatic hypotension (dizziness, weakness, systolic BP ranging from 80 mmHg to 90 mmHg, and diastolic BP ranging from 50 mmHg to 60 mmHg with no orthostasis) and a history of recurrent episodes of dull, pressure, non-stabbing chest pain that occurred sporadically with exertion and usually relieved with sublingual nitroglycerin application was presented to our practice. He had angiographic absence of obstructive CAD (ie, normal epicardial coronary arteries, but small vessel disease). His electrocardiogram showed normal sinus rhythm and a rate of 80 beats per minute. Previous evaluations of his hypotension revealed no evidence of endocrine or autonomic dysfunction. His physical examination and laboratory evaluation including complete blood count were within normal limits. The patient was a non-smoker, did not use alcohol or illicit drugs, and was not on any medication. He requested PDE-5 inhibitor therapy for symptoms of ED. His IIEF-5 score was 17, representing mild ED.

The patient was advised of the need to discontinue using nitrates if he wanted to use a PDE-5 inhibitor because of the known interactions and contraindications of concomitant use. The patient expressed concern about his episodes of recurrent

chest pain and asked for an alternative therapy to control his angina symptoms. The patient did not receive a beta-blocker or calcium channel antagonist because of his symptomatic hypotension. Ranolazine 500 mg orally twice daily was initiated, and the patient was counseled not to resume use of sublingual nitroglycerin when using the PDE-5 inhibitor, sildenafil. At his 6-month follow-up, the patient reported fewer episodes of chest pain since he had been taking ranolazine. In addition, when he had taken sildenafil on a few occasions, his ED improved with an IIEF-5 score of 21. His dizziness secondary to hypotension was completely alleviated once the patient was changed to ranolazine.

Discussion

The Princeton II consensus guidelines on sexual dysfunction and cardiac risk recommend the following:¹⁶ (1) All men with ED should undergo a full medical assessment to evaluate baseline physical activity and cardiovascular risk. Those with low or intermediate cardiovascular risk can seek outpatient or primary care for management of their ED; (2) Men receiving PDE-5 inhibitors who develop angina during sexual activity should stop to see if the pain resolves; if not, emergency care should be sought; and (3) Those seeking emergency care should inform all health care providers of the PDE-5 therapy taken, so that nitrates can be avoided. In this situation, non-nitrate antianginal/anti-ischemic agents can be used, including beta-blockers, calcium antagonists, aspirin, heparin, and statins. If the patient has taken a short-acting PDE-5 inhibitor such as sildenafil or vardenafil, nitrates may be restarted 24 hours after the PDE-5 inhibitor was taken. If the long-acting PDE-5 inhibitor tadalafil was taken, resumption of nitrates should be delayed for at least 48 hours.¹⁶ Therefore, careful attention should be paid to the treatment regimen of the patient in order to avoid nitrate use with PDE-5 inhibitor therapy. If PDE-5 inhibitor use is expected to be continuing on a routine basis, there are no contraindications to using ranolazine as a concomitant antianginal therapy.

Here we report three cases of men with angina pectoris and ED who were either switched from nitrate use to ranolazine or started on ranolazine instead of nitrates, in order to enable vasoactive treatment for ED using PDE-5 inhibitors. All patients reported improved sexual function with PDE-5 inhibitors and control of anginal symptoms with ranolazine. Ranolazine is known to be a viable treatment alternative to standard nitrate use and should be considered, particularly in men seeking medical treatment for ED.

Additive pharmacologic effects of nitrates and PDE-5 inhibitors taken concomitantly have produced serious adverse events including fatalities in patients. Many patients with CAD will have systemic vascular disease that contributes to the likelihood that they will have some degree of ED and will require treatment for both conditions. One approach to the management of these comorbid conditions is to discontinue nitrates and initiate treatment for CAD with beta-blockers or calcium channel



antagonists; however, beta-blockers have also been associated with increasing the frequency of ED. We decided to use ranolazine as another treatment option in these three cases. Ranolazine is an antianginal agent that has a novel mechanism of action, late sodium current inhibition. Data from several randomized, placebo-controlled trials show that ranolazine improves exercise tolerance and reduces anginal frequency, time to onset of ST-segment depression, and recurrent ischemia in patients with chronic angina.^{21–23} without significantly affecting cardiac hemodynamic parameters (heart rate, BP, peripheral vascular resistance, and cardiac output). The most frequently reported adverse events in clinical trials of patients with CAD and chronic angina receiving ranolazine were dizziness, headache, constipation, and nausea.^{23,24} Ranolazine reduces intracellular sodium and produces a consequent reduction in myocyte intracellular calcium.²⁵ If this reduction systemically affects calcium-sensitive potassium channels in the corpus cavernosum, there is the potential for antagonistic interaction of the smooth muscle relaxation produced by PDE-5 inhibitors. However, there are currently no contraindications to the concomitant use of ranolazine with PDE-5 inhibitors. The three patients in these cases were able to discontinue nitrate therapy and have their angina symptoms successfully controlled with ranolazine, which allowed them to receive simultaneous PDE-5 inhibitor therapy to improve their erectile functioning. Ranolazine is metabolized through the cytochrome P450 CYP3A pathway and may increase the plasma concentrations of sensitive CYP3A substrates and drugs with a narrow therapeutic range.²⁴ Published studies in humans describing the concomitant use of PDE-5 inhibitors with ranolazine are lacking. Although the combination of these two compounds might be clinically beneficial for patients with chronic angina along with ED, long-term outcomes, including adverse effects and drug interactions, need to be further evaluated.

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Author Contributions

Conceived and designed the experiments: ERS. Analyzed the data: DUU. Wrote the first draft of the manuscript: DUU. Contributed to the writing of the manuscript: ERS. Agree with manuscript results and conclusions: DUU, ERS. Jointly developed the structure and arguments for the paper: DUU, ERS. Made critical revisions and approved final version: DUU, ERS. Both authors reviewed and approved of the final manuscript.

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