Myocardial Ischemia Following Intracavernous Injection

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ABSTRACT

Erectile dysfunction is a form of male sexual dysfunction affecting 30 million men in the United States.1 Due to efficacy, ease of use, and favorable side effect profile, phosphodiesterase inhibitors are the first line therapy for erectile dysfunction.1,2 Other treatment options include intracavernous injection, testosterone replacement, vacuum devices, and penile prosthesis.2 Despite the efficacy of alternative therapies,2 associated side effects may be potentially life-threatening as suggested by the following case.

A 62-year-old Caucasian male presented to the emergency department with substernal chest pain after intracavernous injection of phentolamine, papaverine, and atropine for erectile dysfunction. This form of therapy was initiated after tadalafil was ineffective. The patient was diagnosed with a non-ST elevation myocardial infarction attributed to his erectile dysfunction therapy. Although causality in this case cannot be established definitively, clinicians should be cognizant of the potential risk for myocardial ischemia with intracavernous combination therapy.

CASE PRESENTATION

A 62-year-old Caucasian male presented to the emergency department with substernal chest pain after intracavernous injection of a standard dose of phentolamine, papaverine, and atropine for erectile dysfunction. This form of therapy was initiated by a men’s health clinic after first line therapy with a phosphodiesterase inhibitor, tadalafil, was ineffective. The patient developed chest pain, palpitations, lightheadedness, and bilateral hand numbness within 20 minutes of a self-administered intracavernous injection. One month prior, the patient had a similar, less severe episode of chest pain after intracavernous injection for which he did not seek treatment.

On the day of admission, he was found by emergency medical responders to be afebrile with a heart rate of 180 beats per minute (bpm) and a blood pressure of 100/60 mmHg. In the emergency department, heart rate and blood pressure improved to 83 bpm and 130/82 mmHg, respectively, following administration of intravenous fluids. Physical examination was within normal limits. Electrocardiogram revealed sinus tachycardia with a heart rate of 126 bpm, left axis deviation, and no significant ST or T wave changes (Figure 1).
Figure 1. Sinus tachycardia, left axis deviation, and no significant ST or T wave changes.

Figure 2. Normal sinus rhythm, left axis deviation, and no significant ST segment elevation or T wave inversions.
Laboratory studies were significant for elevated troponin I at 0.677 ng/ml. Cardiology was consulted and a diagnosis of non-ST elevation myocardial infarction was made. During admission, troponin peak was 1.740 ng/ml. Repeat electrocardiogram on the first day of hospitalization revealed normal sinus rhythm with a heart rate of 65 bpm, left axis deviation, and no significant ST segment elevation or T wave inversions (Figure 2).

Cardiac catheterization revealed no significant coronary artery disease. Echocardiogram demonstrated mild left ventricular hypertrophy, stage 1 diastolic dysfunction, mild anteroseptal and anteroapical wall hypokinesis, and reduced systolic function with left ventricular ejection fraction of 40-45%. The patient was discharged on the third day of hospitalization.

**DISCUSSION**

Phosphodiesterase inhibitors are first line therapy for erectile dysfunction due to efficacy, ease of use, and favorable side effect profile. For patients in whom phosphodiesterase inhibitor therapy has failed or is contraindicated, second line therapies include intracavernous injection (Figure 3), testosterone replacement, vacuum devices, and penile prosthesis. Intracavernous injection therapy has a relatively high success rate in the treatment of erectile dysfunction. A randomized, controlled, double-blind study published in the *Journal of Urology* demonstrated an 82.8% erectile response rate with intracavernous injection of papaverine and phentolamine. Despite this response rate, there is a high attrition rate attributed to penile pain with self-injection. Other side effects of intracavernous combination therapy include injection site bruising, subcutaneous hemorrhage, and prolonged erection. Dose-dependent fibrotic reactions presenting as penile nodules, plaques, or induration may also occur. The only reported systemic side effects are elevated liver enzymes, arterial hypotension, and headache. Since side effects are generally mild and infrequent, intracavernous injection therapy has been deemed safe and effective in the treatment of erectile dysfunction.

The literature supports the use of intracavernous injections as an alternative for the treatment of erectile dysfunction in patients with cardiovascular disease. A study published in the *International Journal of Impotence Research* evaluated erectile response to three intracavernous injection protocols in patients with known cardiovascular disease and failed or contraindicated phosphodiesterase inhibitor therapy. Cardiovascular disease in the study population included hypertension, angina, myocardial infarction, congestive heart failure, valvular heart disease, and arrhythmia. Cardiac interventions the study population had undergone included cardiac
catheterization, coronary artery bypass grafting, and valvular replacement. Protocol I combining papaverine and phenolamine had a 57.5% erectile response rate. Protocol II combining papaverine, phenolamine, and prostaglandin E1 had a 71.1% erectile response rate. Protocol III combining papaverine, phenolamine, prostaglandin E1, and atropine had a 53.8% erectile response rate. These findings support the use of combination intracavernous injection therapy in the treatment of erectile dysfunction in patients with cardiovascular disease.

As a non-selective, competitive alpha adrenergic antagonist, phenolamine causes vasodilation and increased blood flow to enhance erection. Hypotension following administration of phenolamine has been associated with cardiac arrhythmias and myocardial infarction. Papaverine is a smooth muscle spasmylytic and may depress the myocardium, compromise cardiac conduction, and lead to life-threatening arrhythmias. The therapeutic effect of atropine is counterintuitive in the treatment of erectile dysfunction given its antagonism of acetylcholine at parasympathetic sites in smooth muscle. The literature suggests that atropine increases the synergism of the medications used in combination intracavernous injection therapy. Atropine may induce hypertension and tachycardia with risk for arrhythmias, myocardial ischemia, and infarction.

Treatment of erectile dysfunction may increase the risk of myocardial infarction due to physical exertion during sexual intercourse. In this case, if the patient had engaged in intercourse after self-administration of intracavernous injection therapy, he would have been at risk for developing demand ischemia. With the systemic hypotensive effects of intracavernous injection therapy, myocardial oxygen supply would have been compromised. With physical exertion, myocardial oxygen demand would have been increased. This would have led to a mismatch between myocardial oxygen supply and demand. This mismatch, known as demand ischemia, occurs in the absence of a primary acute coronary thrombotic event. Since cardiac catheterization revealed no significant coronary artery disease, demand ischemia may have been the underlying mechanism in this patient’s case.

In patients with underlying coronary artery disease, the systemic hypotensive effects of intracavernous injection therapy could theoretically lead to coronary steal. This phenomenon is often described in the setting of vasodilator stress radionuclide myocardial perfusion imaging. Coronary steal is characterized by a decrease in flow distal to an area of stenosis in response to coronary vasodilation. This may lead to a perfusion defect and myocardial ischemia. By this mechanism, patients with underlying coronary artery disease using intracavernous injection therapy could be at risk for developing myocardial ischemia.

In the literature, there have been two reported cases of myocardial ischemia with intracavernous injection therapy. In the first case, intracavernous injection of alprostadil for penile rehabilitation following radical prostatectomy resulted in unstable angina. This effect was observed at the low dose of alprostadil indicated for penile rehabilitation. Coronary angiography revealed significant coronary artery stenosis requiring percutaneous coronary intervention. The authors hypothesize that alprostadil had a systemic hypotensive effect on the coronary arteries and that myocardial ischemia was caused by the associated decrease in coronary blood flow. This effect was more pronounced due to the patient’s underlying coronary artery disease. This proposed mechanism parallels the aforementioned coronary steal phenomenon and suggests potential risk for myocardial ischemia with intracavernous injection therapy, especially in patients with coronary artery disease.
In the second case, a paraplegic patient developed a myocardial infarction following intracavernous injection of alprostadil for erectile dysfunction. The patient experienced this adverse event following intracavernous administration of a six microgram dose of alprostadil. While the authors do not propose a mechanism by which alprostadil may have caused this patient’s infarction, they note that adverse cardiovascular effects had been reported in five other patients using intracavernous alprostadil for erectile dysfunction. These effects included palpitations, angina exacerbation, complete heart block, and myocardial infarction. They identified patients at greatest risk for experiencing adverse cardiovascular effects with alprostadil as those over the age of 50 with preexisting cardiac disease or hypertension.

In the literature, there have been no reported cases of intracavernous injection of phenolamine, papaverine, and atropine in combination for erectile dysfunction causing myocardial infarction. In fact, the literature supports the use of intracavernous injection therapy for patients with known cardiovascular disease who have failed phosphodiesterase inhibitors or for those in whom phosphodiesterase inhibitor therapy is contraindicated. In light of the systemic hypotensive effects of combination intracavernous injection therapy on the myocardium, there is a theoretical risk for ischemia. Although we are unable to establish causality at this time, the potential risk for myocardial ischemia should be considered by physicians and communicated to patients.

LEARNING POINTS

1. Phosphodiesterase inhibitors are first line therapy for erectile dysfunction. For patients who have failed phosphodiesterase inhibitors or for those in whom phosphodiesterase inhibitors are contraindicated, intracavernous injection has been considered an effective second line therapy.

2. The literature supports the use of intracavernous injection therapy in patients with underlying cardiovascular disease in whom first line therapy has been unsuccessful or contraindicated.

3. Intracavernous injection therapy with phenolamine, papaverine, and atropine may be associated with increased risk of myocardial ischemia. Physicians should be aware of this potential risk and inform their patients accordingly, especially those with preexisting cardiovascular disease seeking an alternative to phosphodiesterase inhibitors.

REFERENCES


