Case Report

Acute Myocardial Infarction: After Sildenafil Citrate Ingestion

MA Rahman[1], S Hoque[2], MJ Haque[3], MS Rahman[4], SMM Zaman[5], MAR Khan[6]

Abstract
Here, we report the occurrence of acute myocardial infarction (MI) associated with the intake of oral sildenafil (Viagra) in a nitrate-free patient without previous history of coronary artery disease. A 48 years old man without previous documented coronary artery diseases developed acute myocardial infarction 30 minutes after ingestion of sildenafil citrate 100 mg that increased in severity during sexual act. Subsequent angiography showed 60% lesion in midsegment of Left Circumflex artery (LCX) artery. Sildenafil-associated MI is rarely seen in patients without documented coronary artery disease. By inhibiting phosphodiesterase type 5, sildenafil can cause an increase in cyclic guanosine monophosphate levels, which mediates the relaxation of vascular smooth muscle in the corpus cavernosum. Athough sildenafil can cause a major decline in systemic arterial pressure in the existence of organic nitrates, physicians should be aware of its adverse cardiovascular effects even in nitrate-free patients. The Naranjo probability scale indicates that sildenafil was the possible cause of the MI. This report shows a rare sildenafil-associated MI in a nitrate-free patient without a previous history of coronary artery disease

Introduction

A 48 years old diabetic and hypertensive patient was admitted to CCU department of Sir Salimullah Medical College, Mitford Hospital, Dhaka, with sudden severe retrosternal chest pain for 1 hour, compressive in nature, radiating to both sides of chest and both upper limbs, associated with nausea, vomiting, sweating, The patient developed this kind of chest pain for the first time, approximately 30 minutes after taking sildenafil 100 mg before a sexual contact, and increasing in severity during sexual act. His high blood pressure, and Diabetes type-2 controlled with oral drugs, was the only remarkable history in his medical record. He denied previous episodes of angina, exertional dyspnoea or nitrate consumption. On clinical examination vital signs were normal.

His ECG showed ST segment elevation in lead I and AVL. (FIG: 1) Troponin-I was 5.6ng/ml, clinically he was diagnosed as a case of high lateral acute MI, and therapy with aspirin, clopidogrel, metoprolol, and thrombolysis with streptokinase (1.5 million) was initiated. Angiography was done after 6 days of admission, showed 60%-lesion in mid segment of LCX and minor irregularities involving Left Anterior Descending (LAD) and Right Coronary artery (RCA) The patient was discharged after one week of admission with advice to do Percutaneous Transluminal Coronary Angioplasty (PTCA) in LCX.

According to Naranjo (ADR) probability scale, the score is 4 for this case, so we can say that sildenafil is a possible cause of Acute MI for this patient

Discussion

Sildenafil was the first Phosphodiesterase type 5 (PDE5) inhibitor approved for the treatment of erectile dysfunction (ED) by the Food and Drugs Administration (FDA), in the United States of

1. Dr. Md. Afzalur Rahman, Professor, Department of Cardiology, Sir Salimullah Medical College & Mitford Hospital, Dhaka.

2. Dr. Sania Hoque. Clinical Assistant, Department of Cardiology, Sir Salimullah Medical College & Mitford Hospital, Dhaka.

3. Dr. Md. Jahurul Haque, Associate Professor, Department of Cardiology, Sir Salimullah Medical College & Mitford Hospital, Dhaka.

4. Dr. Md. Shahinur Rahman, Assistant Professor, Department of Cardiology, Sir Salimullah Medical College & Mitford Hospital, Dhaka.

5. Dr. SM Mustafa Zaman, Assistant Professor, Department of Cardiology, BSMMU, Shahbag, Dhaka.
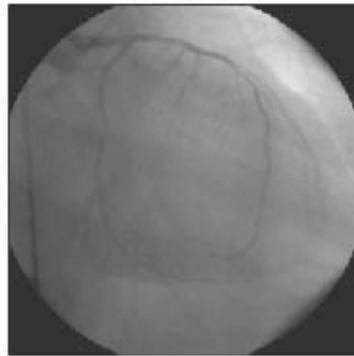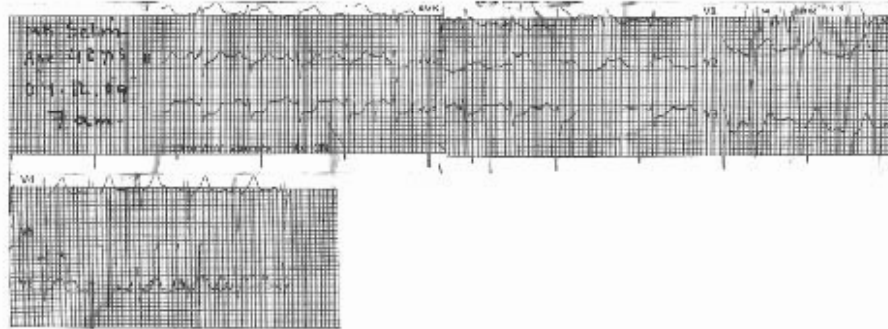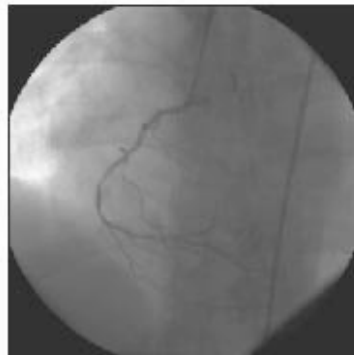
6. Dr. Md. Anisur Rahman Khan, Assistant Professor, Department of Cardiology, Sir Salimullah Medical College & Mitford Hospital, Dhaka.

Showed 50% lesion in LCX and minor irregularities in LAD

Showed minor irregularities in RCA

America (USA) and later by the European Medicines Evaluation Agency.[1] A number of adverse effects-like headache, facial flare (flushing), nasal congestion, visual alterations, dyspepsia, diarrhea, dizziness and rash can occur after sildenafil ingestion.[2] Headache, nasal congestion, and face flare, following its administration, suggests its activity not only at the corpus cavernosum level. Sildenafil can cause Blood flow redistribution, results in a quick drop of peripheral vascular resistance, that could modify normal coronary perfusion and cause myocardial ischemia.[3] Pre-existing vascular coronary damage increases risk to suffer this kind of processes.

The use of nitrates causes universal vasodilatation as the result of an increase of the levels of nitric oxide (NO), contributed by sildenafil, causing an important fall of arterial pressure. Subsequently, arterial blood flow redistribution can lead to a phenomenon consisting of decreasing coronary blood supply and start out a cardiac ischemic ailment[4], In consequence, therapy with nitrates is absolutely contraindicated with sildenafil medical prescription[5,6] Due to the high prevalence of old patients and long expectancy life of patients with diseases, previously mortals, ED presents a high prevalence nowadays. As it is one of the most efficient methods to treat the disease, the prescription of these drugs has suffered an exponential increase. At the end of 2000, more than 10 million people were treated with sildenafil.[5]

Sildenafil therapeutic efficiency has been proven for the treatment of ED caused by both etiologies: primary and secondary to radical prostatectomy, radiotherapy, diabetes mellitus, spinal cord lesion and Parkinson disease[5]. Guidance's for sildenafil management in patients suffering cardiovascular disease, published by American Journal of Cardiology[5], recommend classifying patients prior to its use into three risk groups: low risk; intermediate risk and high risk patients. Only in high risk patients, a cardiovascular evaluation before taking sildenafil is required.[5] In the other cases, it is considered a safe drug.

American College of Cardiology and American Health Association has defined sildenafil potential cardiovascular adverse effects (sudden death, acute myocardial infarction, and ventricular arrhythmias).The manufacturer has inserted a

warning in the prescribing information and a careful prescription of this drug has been promoted for patients with antecedents of coronary ischemia, heart failure, low arterial pressure, multiple antihypertensive or using drugs that interfere sildenafil metabolism.[6]

Involves more than 30 million men only in USA.[5,6] The worldwide prevalence in 1995 was of 152 million. Due to the population ageing, it is expected that in 2025 about 322 million people will be affected.[7] In men 40 years or older ED prevalence reported is equal or higher than 30%.

PDE5 enzyme is one of the 11 isoenzymes known in human organism. It is located in smooth muscle cell and predominates in penis corpus cavernosum. However, its presence in other tissues, such as in canine cardiomyocyte[8], has been reported. This enzyme turns 3´, 5´-cyclical guanosine monophosphate (GMPc) in 5´guanosine monophosphate (5´GMP). GMPc, via a specific kinase protein, allows to exit the intracellular calcium, causing a relaxation state and vasodilatation, followed by a blood flow increase. This is essential to achieve full erection. Sildenafil acts inhibiting PDE5 in a specific way, with a relative low crossed reaction with other PDE. Its chemical structure is similar to GMPc, so inhibits the union between PDE5 with GMPc (at the catalytic enzymatic site), causing its accumulation in the erectile tissue.[9] Two additional agents of the same family have been developed in recent years: Tadalafil and Vardenafil.

Recent clinical researches with both, human beings and animals, have demonstrated that its vasodilator properties and the biochemistry reaction resulting from its action, have beneficial effects to treat diseases such as pulmonary hypertension[9], congestive heart failure and endothelial dysfunction.[9] Cardioprotective effects have been confirmed due to a myocardial pre-conditioning effect, decrease of ischemic risk[9]; in experimental animals models have been reported.

Some authors have recommended to use low doses initially[10] (initial low-quantity doses test) as an efficient and useful measure, instead of effort test or arterial pressure continuous monitoring after sildenafil consumption, to avoid fatal adverse reactions (ischemic episodes, first dosis reaction, hypotension, etc.). We reported here a

case of acute myocardial infarction after the ingestion of 100 mg. of sildenafil, that increased with sexual intercourse without previous history of CAD or nitrates consumption, having coronary artery stenosis (Lcx-60% lesion) documented by angiography.

The FDA reported more than 100 deaths between patients who were prescribed sildenafil during the first months of commercialization of the product.[10] Half of them were due to cardiac events and less than a quarter of them due to AMI. Thirteen months after the arrival of the medication, the number of deaths could increase till more than 50010; however, it is an unknown fact if these events were caused by medication or they were due to an underlying cardiovascular disease coronary angiography.

AMI and death rates analysis in patients using sildenafil are controversial.[9,10] Some of them support its cardiac safety while others defend its causal effect in myocardial ischemia, resulting from mechanisms described above. The truth is that the actual incidence of this kind of events is unknown due to the big number of people that have access to this drug, under reported of fatal adverse reactions and to the absence of serious epidemiologic studies which could evaluate the incidence in consumers.[10]

Supporting the precedent ideas, Herrmann et al., succeeded demonstrating that sildenafil has not direct adverse cardiovascular effects in patients with stable coronary disease in a study with human beings.[11]

The relationship between atherosclerosis and endothelial dysfunction has been proposed as the underlying mechanism that explains the high association between ED and coronary disease. Montorsi et al.[12] have suggested that atherosclerosis is directly related with variable signs depending on the artery that is affected (size of artery hypothesis). Erectile Dysfunction is frequently a sign preceding coronary disease due to the minor size of cavernous arteries compared with coronary arteries.[11,12] Clinical data show how patients with ED, have a 20% of probabilities of suffering concomitant coronary arterial disease, while 60% patients with coronary arterial disease, show ED at the diagnosis.

Shakir et al. demonstrated a decrease of mortality

in a cohort of patients treated with sildenafil in comparison with general United Kingdom population, although it is thought that the results could be slated by the under reported of events.[13]

Conclusion

Emotional arousal induced by sildenafil, followed by the heavy physical exertion during sexual activity, triggers plaque rupture that leads to acute myocardial infarction. This is a case report of a patient suffering from AMI after sildenafil intake, without previous use of nitrates or documented coronary artery diseases. Although some studies have suggested the absence of a hemodynamic relationship between the use of this family of drugs and coronary disease, additional studies looking for the psychopathological explanations in those cases of AMI associated to sildenafil uses are required. The Naranjo probability scale indicates that sildenafil was the possible cause of the MI for our patient. Each time more of these cases are reported in literature. While new data are compiled, it is recommended to keep under observation potential adverse effects of sildenafil on coronary circulation when prescribed, principally in patients with risk of coronary disease or those using vasodilator drugs such as nitrates. We suggest that patients are to be clearly informed about risks and benefits of the use of sildenafil. Low dose of sildenafil should be advised when therapy is initiated among the elderly population.

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