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Egyptian Pharmaceutical Vigilance Center (EPVC)

Pharmacovigilance Department

Inside this issue:

Case report from Cairo-STEMI (ST-segment elevation myocardial infarction) in male Patient associated with Sildenafil

The regional center in Cairo received a yellow card concerning a sixty seven Years old male, who were administrating Sildenafil 100 mg daily for his erectile dysfunction.

Patient was admitted to the hospital with anterior ST-Elevation Myocardial Infarction (STEMI), he received streptokinase that failed, underwent rescue PCI, Coronary angiography revealed normal (LMCA)

Medical History: Patient is smoker, not diabetic or hypertensive.

STEMI: ST-Elevation Myocardial Infarction is a very serious type of heart attack during which one of the heart's major arteries is blocked. ST-segment elevation is an abnormality detected on the 12-lead ECG

PCI: Percutaneous coronary intervention also known as coronary angioplasty, is a nonsurgical technique for treating obstructive coronary artery disease, including unstable angina, acute myocardial infarction (MI), and multi-vessel coronary artery disease (CAD)

LMCA: left main coronary artery

Labeled information:

According to Sildenafil Summary of product Characteristics (SmPC)

It was stated under section dosing information and Therapeutic indications, the following:

Usual Adult Dose for Erectile Dysfunction:

Initial dose: 50 mg orally once a day, as needed, 1 hour prior to sexual activity
Maintenance: 25 to 100 mg orally once a day, as needed, 1 hour prior to sexual activity

The maximum recommended dosing frequency is once per day.

Usual Geriatric Dose for Erectile Dysfunction: [1, 2]

Initial dose: 25 mg orally once a day 1 hour prior to sexual activity

The maximum recommended dosing frequency is once per day.

It was stated under section Side effects that:

It may cause Serious Cardiovascular Side effects such as:

-Uncommon (0.1% to 1%): palpitations, tachycardia, hypertension, hypotension
-Rare (less than 0.1%): Myocardial infarction, atrial fibrillation, sudden cardiac death, ventricular arrhythmia, unstable angina

-Frequency not reported:, angina pectoris, AV block, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy, shock

-Post marketing reports: Serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction; sudden cardiac death; ventricular arrhythmia; cerebrovascular hemorrhage; transient ischemic attack; hypertension; subarachnoid, intracerebral, and pulmonary hemorrhage have been reported in temporal association with the use of this drug

Recommendations for Healthcare Professionals:

- Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients and consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects
- Use with caution in patients with the following underlying conditions:
    - Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months
    - Patients with resting hypotension (BP <90/50 mmHg) or hypertension (BP >170/110 mmHg)
    - Patients with cardiac failure or coronary artery disease causing unstable angina.
- In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

References:

1. Drugs.com: Viagra side effects (Click here)
2. Medicines.org.uk: Viagra 100 mg Summary of Product Characteristics (SPC) - (eMC) (Click here)
3. Medscape: Percutaneous Coronary Intervention (PCI) (Click here)

Case report from Alexandria- death due to uncontrolled hemorrhage associated with Enoxaparin administration

The regional center in Alexandria received an ICSR concerning 16 years old male patient suffered from DVT which was associated with ICE (Ifosfamide, Carboplatin and Etoposide) chemotherapy protocol developed massive uncontrolled hemorrhage after Enoxaparin administration for about 5 months.

Patient was administering ICE protocol as treatment for rhabdomyosarcoma. Then he developed DVT which was treated by Enoxaparin 60mg/12hrs. treatment Started in 11/2015 till his death on

15/04/2016 due to massive uncontrolled bleeding that led to his admission to the ICU where physician stopped enoxaparin and tried to manage the case but unfortunately the patient developed also febrile neutropenia which was treated by antibiotics, antifungals and dexamethasone, at the end physicians couldn't rescue him and he died 2 or 3 days later on 15/04/2017.

N.B: ICE chemotherapy protocol (administered protocol) was discontinued before this massive bleeding by more than 1 month.

Suspected Drugs:

Enoxaparin is a Low Molecular Weight Heparin (LMWH) has a small effect on the activated partial thromboplastin time and strongly inhibit factor Xa. Enoxaparin is derived from porcine heparin that undergoes benzylation followed by alkaline depolymerization. Enoxaparin has a higher ratio of antifactor Xa to antifactor IIa activity than unfractionated heparin.

Reaction (Hemorrhage): a loss of a large amount of blood in a short period, either externally or internally. Hemorrhage may be arterial, venous, or capillary.

Underlying disease (DVT):

Deep vein thrombosis (DVT) refers to thrombus formation in the deep veins of the extremities, most commonly the lower extremities. Proximal DVTs are more serious than distal DVTs.

Labeled information:

According to **Enoxaparin sodium Pre-filled syringe** Summary of product Characteristics **(SmPC)** it was stated under section 4.8 **Undesirable effects** that

haemorrhages were the most commonly reported reaction. *These included major haemorrhages, reported at most in 4.2 % of the patients (surgical patients). Some of these cases have been fatal.*

As with other anticoagulants, haemorrhage may occur during enoxaparin therapy in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the concomitant use of medications affecting haemostasis. The origin of the bleeding should be investigated and appropriate treatment instituted.

Treatment in patients with DVT with or without PE:

Very common :Haemorrhage(such as haematoma, ecchymosis other than at injection site, wound haematoma, haematuria, epistaxis and gastro-intestinal haemorrhage)

Uncommon :Intracranial haemorrhage, Retroperitoneal haemorrhage

Recommendations for Healthcare Professionals:

- Based on consensus, incidental pulmonary embolus (PE) and deep vein thrombosis (DVT) should be treated in the same manner as symptomatic VTE.
- LMWH is preferred over unfractionated heparin(UFH) for the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed venous thromboembolism (VTE) who does not have severe renal impairment (dosage adjustment needed if creatinine clearance <30 mL/min) .
- Enoxaparin dose is 1 mg/kg every 12 hours to 1.5 mg/kg daily (For cancer patients and those at high bleeding or thrombosis risk, favor twice -daily dosing)
- Use of novel oral anticoagulants for either prevention or treatment of VTE in patients with cancer is not recommended at this time.
- In patients with cancer, warfarin is not preferred due to the higher risk of recurrent thromboembolism (16% to 17%) compared with LMWH (7% to 9%) after 6 months to 1 year of use. The risk of bleeding is the equivalent in **cancer patients with warfarin or**

LMWH, and American Society of Clinical Oncology guidelines recommend LMWH over warfarin in patients with cancer.

Warfarin (Vitamin K Antagonist(VKA)) is an acceptable alternative for long-term therapy if LMWH is not available with a targeted **INR of 2 to 3**.

- As there is a risk of antibody-mediated heparin-induced thrombocytopenia also occurring with low molecular weight heparins, **regular platelet count monitoring should be considered prior to and during therapy with these agents.** Thrombocytopenia, usually appears between the 5th and the 21st day following the beginning of therapy. In practice, if a confirmed significant decrease of the platelet count is observed (30 to 50 % of the initial value), enoxaparin sodium treatment must be immediately discontinued and the patient switched to another therapy.
- Heparin can suppress adrenal secretion of aldosterone leading to **hyperkalaemia**, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma potassium or taking potassium sparing drugs. The risk of hyperkalaemia appears to increase with duration of therapy but is **usually reversible**. Plasma potassium should be measured in patients at risk before starting heparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days.
- The anticoagulant effects can be largely neutralised by the slow intravenous injection of Protamine, but even with high doses of **Protamine,** the anti-Xa activity of enoxaparin sodium is never completely neutralised (maximum about 60%).in the first 8 hours after enoxaparin administration 1mg Protamine should neutralise the effects of 1mg of enoxaparin. maximum recommended Protamine dose is 50mg. Decisions regarding the necessity and dose of subsequent Protamine injections should be based on clinical response rather than measurement of anti Xa or anti XIIa results.

References:

1. *Enoxaparin (Lexi-Drugs Multinational) (Click here)*
2. *Hemorrhage*, medical dictionary, *(Click here)*
3. *American Society of Clinical Oncology Guideline: Recommendations for Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer (Click here)*
4. *2011 Clinical Practice Guide on Anticoagulant Dosing and Management of Anticoagulan tAssociated Bleeding Complications in Adults (Click here)*

Impairment of performance in a test of learning and memory induced by using Remeron and Apexidone during the treatment of irritable bowel syndrome (IBS)

The Egyptian pharmaceutical Vigilance regional center in Sohag has received an ICSR for Adult male patient 40 years old, who had a history of severe abdominal cramping, bloating, and constipation, his psychologist had diagnosed as irritable bowel syndrome and prescribed Remeron (half tablet) and Apexidone 1 mg (once daily) since 2012, then he significantly improved, his bowel movements were normal, and he had a marked decrease in all gastrointestinal symptoms

One year later, he suffered from impairment of performance in a test of learning and memory without knowing the reason, at 2016 his psychologist advised to stop taking remeron and apexidone and prescribed piracetam tab as treatment then his memory performance was recovered but he suffered from IBS again so his psychologist re-prescribed remeron again as half tab daily without apexidone and he recovered from IBS with mild memory performance impairment.

Remeron (mirtazapine)Tablets: are an orally administered drug. Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds which is an antidepressant first approved in the Netherlands in 1994 for the treatment of major depressive disorder. However, evidence suggests its effectiveness in a variety of other psychiatric disorders and non-psychiatric medical conditions.

Apexidone: Risperidone (active ingredient) is an antipsychotic medication. It works by changing the effects of chemicals in the brain, Risperidone is used to treat schizophrenia and symptoms of bipolar disorder (manic depression), and it is also used in autistic children to treat symptoms of irritability.

Impairment of performance in a test of learning and memory: state in which a person is unable to reme mber or recall bits of information or behavioral ski lls. Impaired memory may be attributed to pathophysiological or situational cau ses that are either temporary or permanent, you may find it harder to recall information or events, learn new things, or form new memories.

***Upon search it was found that*:**

- In a study in which juvenile rats were treated with oral risperidone from days 12 to 50 of age, a reversible impairment of performance in a test of learning and memory was seen, in females only, with a no-effect dose of 0.63 mg/kg/day, No other consistent effects on neurobehavioral or reproductive development were seen up to the highest testable dose (1.25 mg/kg/day).
- REMERON may impair judgment, thinking, and particularly, motor skills, because of its prominent sedative effect, the drowsiness associated with mirtazapine use may impair a patient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that
- Using Risperidone together with mirtazapine may increase side effects such as dizziness, drowsiness, confusion, and difficulty concentrating.
- Some people, especially the elderly, may also experience impairment in thinking, judgment, and motor coordination.
- You should avoid activities requiring mental alertness such as driving or operating hazardous machinery until you know how the medications affect you.

References:

1. Remeron label -FDA (Click Here)
2. Risperidone label –FDA (Click Here)
3. Drugs.com -Risperdal (Click Here)
4. Drugs interaction report (Click Here)