EGYPTIAN DRUG AUTHORITY

هيئة الدواء المصرية

The Egyptian Pharmaceutical Vigilance center

مركز اليقظة الصيدلية المصري

IN THIS ISSUE

EPVC Mission

Pharmaceutical Vigilance administration is the way through which the processes for authorizing, regulating, monitoring and evaluating the safety of any pharmaceutical product or medical device take place, in addition to disseminating any safety information for public health programs, healthcare professionals, and the

The Pharmaceutical vigilance administration is an integral part of the Central Administration of Pharmaceutical Care that works on the enhancement of the pharmaceutical services to guarantee safe and effective use of medications in Egypt, under the patronage of the Egyptian Drug Authority.

Newsletter

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Bupropion: risk of serotonin syndrome with use with other serotonergic drugs

Bupropion is an antidepressant medication used to treat major depressive disorder and seasonal affective disorder. Cases of serotonin syndrome have been identified in association with bupropion, especially in overdose or when bupropion is administered with other drugs with a serotonergic effect.

Review of risk

Bupropion is a norepinephrine–dopamine reuptake inhibitor (NDRI). Although bupropion mainly has an effect on dopamine and noradrenaline reuptake, there is some published evidence to suggest cross-reactivity between dopaminergic, noradrenergic, and serotonergic signaling in the central nervous system

Serotonin syndrome – signs and symptoms

Serotonin syndrome is an iatrogenic disorder of serotonergic hyperstimulation in which the underlying mechanism is thought to involve excessive stimulation of 5-HT1A receptors. It occurs most commonly when two or more serotonergic agents with different pharmacological mechanisms are administered either concurrently or sequentially without a sufficient washout period. However, it can also be associated with a single serotonergic agent, particularly at a high dose.

Signs and symptoms of serotonin syndrome may include mental-status changes (for example, agitation, hallucinations, coma), autonomic instability (for example, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (for example, hyperreflexia, incoordination, rigidity), and gastrointestinal symptoms (for example, nausea, vomiting, diarrhoea).

Cases of serotonin syndrome have been identified in associated with bupropion, especially in overdose or when bupropion is administered with other drugs with a serotonergic effect.

If serotonin syndrome is suspected, a dose reduction or discontinuation of bupropion therapy should be considered, depending on the severity of the symptoms.

Advice for Patients:

* If you are told you may be at risk of serotonin syndrome, be aware of symptoms, including
  - ⇒ mental status changes (for example, agitation, hallucinations),
  - ⇒ gastrointestinal symptoms (for example, nausea, vomiting, diarrhoea
  - ⇒ body temperature above 38°C
  - ⇒ increase in heart rate
  - ⇒ signs of unstable blood pressure such as facial flushing, headaches, sweating, short periods of dizziness
  - ⇒ exaggeration of reflexes
  - ⇒ muscular rigidity
  - ⇒ lack of coordination
  - ⇒ and talk to your prescriber if you experience these
* Never exceed the prescribed dose of bupropion

Bupropion: risk of serotonin syndrome with use with other serotonergic drugs Continued

In reference to MHRA; Advice for Healthcare Professionals:

- Cases of serotonin syndrome have been reported in association with bupropion and coadministration with serotonergic drugs, for example selective serotonin reuptake inhibitors (SSRIs) serotonin norepinephrine re-uptake inhibitors (SNRI)
- If concomitant prescribing with other serotonergic drugs is clinically warranted: do not exceed the recommended dose
- Remind patients of the milder symptoms of serotonin syndrome at initiation of treatment and at any change of dose and the importance of seeking medical advice if they occur
- Ensure at initiation of bupropion that patients are aware that they should return for a review of their medication, especially if they are also taking medicines for depression (such as SSRI or SNRI),
- If serotonin syndrome is suspected, either decrease the dose of bupropion or withdraw therapy depending on the severity of the symptoms

References:

1. *MHRA (Click here)*
2. *Drugs.com (Click here)*

Case Report from Alexandria: A suggested correlation between Warfarin administration and Acute kidney Injury as Anticoagulant-related nephropathy

The regional center in Alexandria received a yellow card concerning a case where:

A 62 Years old female patient suffering from Atrial fibrillation was administered Warfarin 5 mg tablets once daily and was following up her INR.

On 10 December 2020, the patient was admitted to the hospital suffering from Melena, her INR was above 10 and her hemoglobin was 6.5, her Renal Creatinine increased from 1.6 to more than 2 and was diagnosed with Warfarin Toxicity.

The reporter said that the reaction was life-threatening as the patient was actively bleeding, Warfarin was discontinued immediately. The reporter added that the patient was supposed to be given Fresh Frozen plasma but the specialist in-charge delayed that option and gave the patient 2 Warfarin antidotes (Vitamin K).

The bleeding was resolved after that and her INR was beginning to decrease gradually. The Patient was given Pantoprazole infusion for melena treatment and had a blood infusion of 3 Blood bags.

The patient improved and was discharged on 15 December 2020.

The reporter said that once AKI resolved, Warfarin was continued in most of the cases but in this particular case, the patient was shifted to another anticoagulant drug.

The reporter added that it was not the only case that suffered the same reaction and there may be a correlation between AKI and Warfarin toxicity, where it could be, either ways, Melena happened first which caused dehydration that resulted in AKI or that AKI happened at first which resulted in Warfarin toxicity that caused bleeding.

No more relevant information was available. The Reporter is a clinical Pharmacist at the hospital.

Background :

Warfarin is commonly called a "blood thinner," but the more accurate term is "anticoagulant." It helps to keep blood flowing smoothly in your body by decreasing the amount of certain substances (clotting proteins) in your blood. [2]

Pharmacologically, Warfarin is known as Anti-thrombotic agent (Vitamin K Antagonist), a synthetic anti-coagulant of the coumarin series and acts by inhibiting the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. [1]

Serum Creatinine is a blood test that measures how well your kidney works. [3]

Your body produces creatinine at a constant rate all the time, and healthy kidneys remove almost all of this creatinine. By comparing the amount of creatinine in your blood with a standard normal amount, your healthcare provider can get a good idea of how well your kidneys are working. [3]

Anticoagulant-related nephropathy (ACRN; also referred to as warfarin-related nephropathy) is a type of acute kidney injury (AKI) that may be caused by excessive anticoagulation with warfarin and other anticoagulants. [4]

Case Report from Alexandria: A suggested correlation between Warfarin administration and Acute kidney Injury as Anticoagulant-related nephropathy continued

Labeled information:

According to warfarin Summary of product Characteristics (SmPC)[5] the following was stated under section **Warnings and Precautions**:

Hemorrhage

Warfarin can cause major or fatal bleeding. Bleeding is more likely to occur within the first month. Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age greater than or equal to 65, history of highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, anemia, malignancy, trauma, renal impairment, certain genetic factors, certain concomitant drugs, and long duration of warfarin therapy.

Perform regular monitoring of INR in all treated patients. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shortest duration of therapy appropriate for the clinical condition. However, maintenance of INR in the therapeutic range does not eliminate the risk of bleeding.

Acute Kidney Injury

In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur with Warfarin, possibly in relation to episodes of excessive anticoagulation and hematuria More frequent monitoring of anticoagulation is advised in patients with compromised renal function."

Recommendations for Healthcare professionals :

1. Acute kidney injury (AKI) resulting from glomerular hemorrhage has been described in patients with underlying kidney disease in the absence and presence of coagulopathy (international normalized ratio [INR] of 6–9 range). More recently, AKI has been described among patients without underlying kidney disease and with more modest elevations of INR. The recognition of a characteristic histologic lesion that was associated with the clinical presentation of otherwise unexplained AKI in the setting of over-anticoagulation led to the term "anticoagulant-related nephropathy.
2. Among patients who develop AKI and are on chronic anticoagulant therapy, a presumptive diagnosis of ACRN should be made if a severe coagulopathy is present and if other causes of AKI have been excluded.
3. The diagnosis of ACRN should be suspected among patients who present with AKI in the setting of excessive anticoagulation and hematuria. A definitive diagnosis is made by renal biopsy.
4. The initiating event in the pathogenesis of ACRN appears to be glomerular hemorrhage, caused by excessive anticoagulation due to warfarin or other anticoagulants. Glomerular hemorrhage results in the formation of obstructing RBC **casts** within the renal tubules. Obstructing intraluminal RBC casts are the most conspicuous histologic feature of ACRN in the tissue obtained from patients who have undergone biopsy.
5. The management of warfarin-related nephropathy (WRN) in patients requiring prolonged anticoagulation poses a management dilemma. Alternative to warfarin, other anticoagulants such as dabigatran (direct thrombin inhibitor) and rivaroxaban, apixaban, and edoxaban (direct-activated factor X inhibitors) are being increasingly used. However, their renal safety is not established.
6. The first case of acute kidney injury and occlusive red blood cell (RBC) tubular casts associated with a high international normalized ratio in a patient receiving warfarin was identified. This entity, named

Case Report from Alexandria: A suggested correlation between Warfarin administration and Acute kidney Injury as Anticoagulant-related nephropathy continued

warfarin-related nephropathy, was later renamed anticoagulant-related nephropathy (ARN) after similar cases with other anticoagulants were described. [6]

7. The underlying molecular mechanism is thought to be warfarin-induced thrombin depletion; however, newer studies have hinted at an alternative mechanism involving reductions in activated protein C and endothelial protein C receptor signaling. Prompt recognition of ARN is critical, as it is associated with accelerated progression of chronic kidney disease, and significant increases in short-term and long-term all-cause mortality.
8. The most important measure to prevent ACRN is proper adjustment of the anticoagulant dose, especially in the CKD patients, who are more vulnerable to ACRN.
9. Given the significant impact of ARN on renal function and all-cause mortality, a thorough understanding of the pathophysiology, molecular mechanisms, clinical spectrum and therapeutic interventions for ARN is crucial to balance the risks and benefits of anticoagulation and optimize treatment. [7]
10. Other independent predictors of AKI risk in these patients were age, diabetes mellitus, heart failure, hypertension, and glomerulonephritis particularly with nephrotic syndrome. Kidney biopsy in a subset of these patients showed obstruction of the renal tubule by RBC casts, and this appears to be the dominant mechanism of AKI
11. In one of the studies conducted on the patients suffered from ACRN, some patients had a complete renal recovery where others had a partial or no renal recovery, estimated Glomerular Filtration Rate was the main Factor differentiating between both groups as the patients with Normal eGRF prior ACRN had a complete renal recovery while those of low eGRF were partially recovered or had no recover at all.
12. Since the renal biopsy is not performed in most cases, the diagnosis is frequently presumptive. (Morphologically, it is characterized by glomerular hemorrhage and acute tubular necrosis due to obstruction by red blood cell casts and, ultimately, by haeme toxicity.) [8]
13. Treatment is mainly supportive and the central approach is prevention, closely monitoring the patients under anticoagulation specially those with underlying risk factors. subset of these patients showed obstruction of the renal tubule by RBC casts, and this appears to be the dominant mechanism of AKI

References:

1. *EMC* (Click here)
2. *WebMD* (Click here)
3. *WebMD* (Click here)
4. *NCBI* (Click here)
5. *RxList* (Click here)
6. *Science direct* (Click here)
7. *PubMed* (Click here)
8. *NCBI* (Click here)

One report counts

A call for reporting

What is Pharmacovigilance

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug- related problem.

What is the Egyptian Pharmaceutical Vigilance Center?

With the increasing demand for patient's safety which is becoming more stringent, . The Egyptian Pharmaceutical Vigilance Center was established to be responsible for the safety monitoring of the pharmaceutical products throughout its lifecycle and it is the regulatory authority regarding Pharmacovigilance and its applications .

EPVC monitors the safety of all types of pharmaceutical products, including human medicines, biological products, supplements, cosmetics, veterinary medicines, medical devices, Biocides and pesticides

Please remember that you can report safety information of medicines to EPVC using the following communication information:

Communication information

The Egyptian Drug Authority (EDA)
Pharmaceutical Care Administration
The Egyptian Pharmaceutical Vigilance Center (EPVC)

Address: 21 Abd El Aziz AlSoud Street. El-Manial, Cairo, Egypt, PO Box: 11451
Telephone: (+2)02 25354100/ (+2)02 23684288/ (+2)02 23648046/ (+2) 02 23640368/ (+2)02 23648769
Extension: 1303
Fax: +202 – 23610497
Email: pv@edaegypt.gov.eg,
pv.followup@edaegypt.gov.eg

Reporting link: www.edaegypt.gov.eg
https://sites.google.com/view/epvc-reporting/healthcare-professional-public-adverse -drug-event-reporting/reporting-other-adverse-drug-event-cases

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