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 Egyptian citizen.

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.

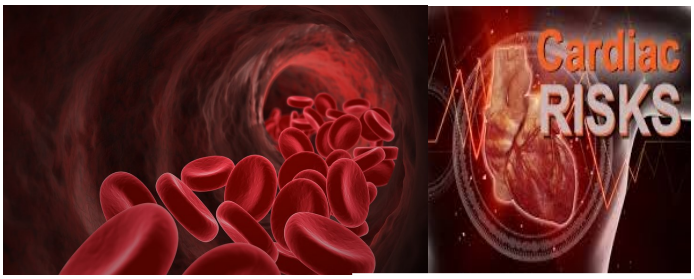
Newsletter

March 2021

Volume 12 Issue 3

Erythromycin: Cardiac Risk (QT interval prolongation) and Drug Interaction with Rivaroxaban

Erythromycin is a macrolide antibiotic that is active against gram-positive cocci and gram-positive bacilli, some gram-negative cocci, and some gram-negative bacilli. It has been associated with events secondary to QT interval prolongation such as cardiac arrest and ventricular fibrillation. In addition, potential drug interaction between rivaroxaban and erythromycin resulting in increased risk of bleeding has also been identified.



Review of risks

It is widely used to treat chest infections such as pneumonia, skin problems, and sexually transmitted diseases. It is used in children, often to treat ear or chest infections.

Regarding cardiac risk: Erythromycin has been associated with events secondary to QT interval prolongation such as cardiac arrest and ventricular fibrillation. Erythromycin should not be given to patients with a history of QT interval prolongation or ventricular cardiac arrhythmia, including torsades de pointes, or patients with electrolyte disturbances. Cardiotoxic effects are recognised with other macrolide antibiotics. Clinicians should be aware of the increased short-term risk of adverse cardiac outcomes, so that the benefits and risks of treatment can be fully evaluated at the time of treatment initiation in each patient, particularly those at high risk of cardiac events.

Regarding interaction with Rivaroxaban: Erythromycin and clarithromycin inhibit CYP3A4 and P-gp and can lead to an increase in the maximum blood concentration of rivaroxaban leading to increased risk of bleeding. All patients prescribed DOACs, including those also on macrolides, should be informed of the signs and symptoms of bleeding and be advised to seek medical advice should they occur.

In reference to MHRA; Advice for healthcare professionals:

* Be aware of reports of cardiotoxicity (QT interval prolongation) with macrolide antibiotics, in particular with erythromycin and clarithromycin
* Erythromycin should not be given to patients with:
  - ⇒ a history of QT interval prolongation (congenital or documented acquired QT interval prolongation) or ventricular cardiac arrhythmia, including torsades de pointes
  - ⇒ electrolyte disturbances (hypokalaemia or hypomagnesaemia due to the risk of arrhythmia associated with QT interval prolongation)
* consider the potential benefit of treatment against the cardiac risks when prescribing in patients at increased risk of a cardiac event; patients in whom caution is needed are those with:
  - ⇒ cardiac disease or heart failure
  - ⇒ conduction disturbances or clinically relevant bradycardia
  - ⇒ those concomitantly taking other medicines associated with QT interval prolongation
* Direct patients to the patient information leaflet and remind at-risk patients of the importance of seeking medical attention if they develop signs or symptoms of a cardiac event
* Erythromycin is widely used in children, some of whom may have QT interval prolongation; therefore, consider the child's medical history and balance the treatment benefits against the potential risks
* Erythromycin may interact with rivaroxaban and increase the risk of bleeding – consider this interaction when prescribing antibiotics and follow precautions in the product information if concomitant use is necessary

References:

MHRA (Click here)

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Local Case Report

Case Report from Alexandria: Furosemide infusion dosing error causing a serious reaction to a Neonate

The regional center in Alexandria had received a yellow card concerning a case of a newly born female neonate 19 days old (weighting 3.5 kgs) hospitalized after suffering from respiratory distress. She stayed in the hospital for 60 days with pneumonia, sepsis and edema. The neonate was under mechanical Ventilation during the first days in the hospital then her condition improved and she was shifted to continuous positive airway pressure (CPAP) which was a progress in her condition as the reporter told (a clinical Pharmacist at the hospital).
During her stay, she was given Furosemide 10 mg/ml ampoule for the edema with dose 0.01 mg/Kg/minute infusion intravenously on 1st of July, which the reporter later told that this dose was very high for the neonate and it was considered as a dose calculation error.

It was explained that the ICU protocol for children was applied which is considered a medication error as this case involved a neonate not a child, and another protocol should have been applied instead.
She added that even the ICU protocol for children was 0.01mg/kg/hour and not per minute as applied to this neonate which made the situation even worse as the baby girl suffered during the Infusion from a serious drop in heart rate followed by oxygen desaturation, shock and Cardiac arrest.

The infusion was stopped at once, ambu bag was used immediately and the neonate was re-ventillated. The reaction was resolved, and the neonate was shifted one more time to Continuous positive airway pressure (CPAP) which was a progress in her condition. She stayed at the hospital till she was totally improved and was normally breastfed by her mother.

For respiratory distress, pneumonia and sepsis, she was given as concomitant drugs:

- Vancomycin 500 mg ampoule with dose 15 mg/kg/dose.
- Meropenem 500 mg vial with dose 20 mg/kg/dose.
- Norepinephrine 4 mg/4 ml with dose 0.2 mg/kg/min.
- Fentanyl 50 mcg/ml ampoule with dose 4 mcg/kg/hour

No more relevant information was available.

Background :

Furosemide : is a sulphonamide derivative [3], a type of medicine called a *Loop diuretic*, a strong diuretic agent of fast action, which is used to treat high blood pressure, heart failure and edema (a buildup of fluid in the body). It is indicated in adults and pediatric patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome [2], and it is the most commonly used diuretic in the newborn period.

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Case Report from Alexandria: Furosemide infusion dosing error causing a serious reaction to a Neonate continued

It comes in the form of tablet and liquid for oral administration. It can also be given by injection, but this is usually only done in hospital. [1]

Diuretics increase the rate of urine flow and Na^+ excretion and are used to adjust the volume and/or the composition of body fluids. The basic urine-forming unit of the kidney is the nephron, which consists of a filtering apparatus, the glomerulus, connected to a long tubular portion that reabsorbs and conditions the glomerular ultrafiltration. [3]

Labeled information:

According to Furosemide Summary of Product Characteristics (SmPC) [4] it was stated under section (***4.8 Undesirable effects***) that:

Cardiac disorders:
In particular, at the initial state of treatment and in elderly, a very intense diuresis may cause a reduction in blood pressure which, if pronounced may cause signs and symptoms such as orthostatic hypotension, acute hypotension, sensations of pressure in the head, dizziness, circulatory collapse, thrombophlebitis or sudden death (with i.m. or i.v. administration).

Pregnancy, puerperium and perinatal conditions:
Premature infants treated with furosemide may develop nephrocalcinosis and/or nephrolithiasis; due to calcium deposit in renal tissue.
In premature infants with respiratory distress syndrome, diuretic treatment in the first weeks of life with furosemide can increase the risk of persistent ductus arteriosus Botalli.

Recommendations for Healthcare professionals :

1. Furosemide is potent diuretic that, if given in excessive amounts, may lead to profound diuresis with water and electrolyte depletion. Careful medical supervision is required; dosing must be adjusted to patient's needs [5]
2. In the very preterm infants, $t_{1/2}$ may be as long as 24 h, making progressive drug accumulation possible with repeated use, and this may be a factor in the increased risk of serious late-onset deafness seen in children exposed to sustained treatment in the neonatal period. Premature neonates <32 weeks postmenstrual age have an increased risk of developing high serum furosemide concentrations due to prolonged $t_{1/2}$ and, therefore, dosing schedules should be adjusted for this age group [7]
3. Depending on the maturity of the kidney, elimination of furosemide may be slow. In case of children with insufficient capacity of glucuronidation, the metabolism of the drug is also reduced. In term neonates the half-life is generally less than 12 hours. [4]
4. The experience in children and adolescents (up to 18 years of age) are limited. The intravenous administration of furosemide to children and adolescents below 15 years is only recommended in exceptional cases. The dosage will be adapted to the body weight, and the recommended dose ranges from 0.5 to 1 mg/kg body weight daily up to a maximum total daily dose of 20 mg. There should be a switch to oral therapy as soon as possible. [4]
5. In case of Furosemide IV Administration, Inject directly or into tubing of actively running IV over 1-2 minutes. Administer undiluted IV injections at rate of 20-40 mg/min; not to exceed

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4 mg/min for short-term intermittent infusion; in children, give 0.5 mg/kg/min, titrated to effect. Use infusion solution within 24 hours. [6]

6. Initial dose of furosemide is 1 mg/kg intravenously with slow push, or intramuscularly. The dose may increase to a maximum of 2 mg/kg per dose intravenously or 6 mg/kg per dose orally. In premature infants administrate furosemide every 24 h, whereas in full term infants administrate furosemide every 12 hr. Neonatal Formulary suggests giving 1 mg/kg of furosemide intravenously or intramuscularly or 2 mg/kg by mouth, repeatable after 12 to 24 h. The drug should not be given more than once every 24 h to infants with postmenstrual age of less than 31 weeks.
7. Premature infants (possible development of nephrocalcinosis /nephrolithiasis; renal function must be monitored and renal ultrasonography performed). In premature infants with respiratory distress syndrome, diuretic treatment with furosemide during the first weeks of life can increase the risk of persistent ductus arteriosus Botalli.
8. The principal signs and symptoms of overdose with furosemide are dehydration, blood volume reduction, hypotension, electrolyte imbalance, hypokalemia and hyperchloremic alkalosis, and are extensions of its diuretic action. [8]
9. Therapy should be individualized according to patient response to gain maximal therapeutic response and to determine the minimal dose needed to maintain that response. [8]

References:

1. *NHS* (Click here)
2. *RxList* (Click here)
3. *NCBI* (Click here)
4. *EMC* (Click here)
5. Medscape (Click here)
6. Medscape (Click here)
7. *NCBI* (Click here)
8. *FDA* (Click here)

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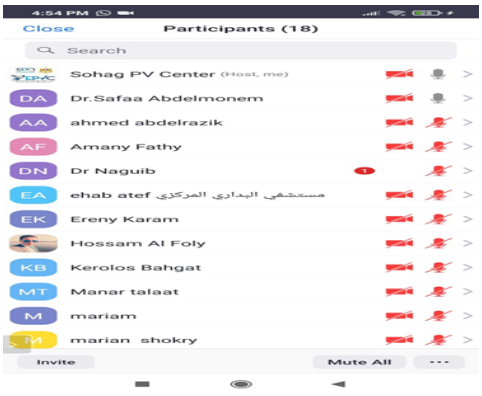
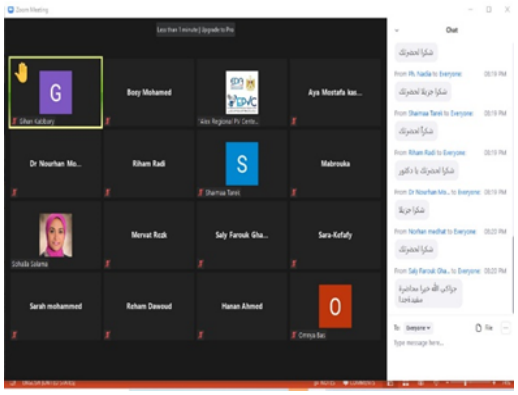
Continuing Awareness raising sessions to Spread Pharmaceutical Vigilance Knowledge

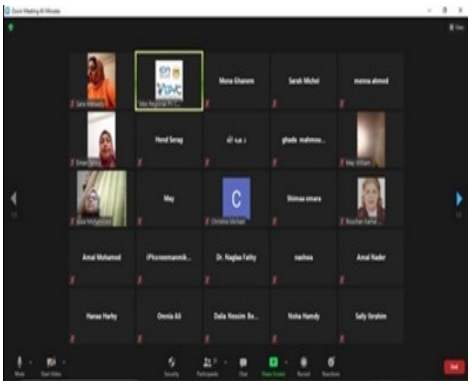
In accordance to the role of the Egyptian Pharmaceutical Vigilance Center (EPVC) in raising awareness of the importance of Pharmacovigilance Science Practice & activation of Adverse Drug Reactions reporting (ADR) of Pharmaceutical Products ,it's Regional Centers (Cairo ,Alexandria & Suhag) Conducted different online sessions for 174 Pharmacists working at health care facilities of Health Directorates of (Alexandria ,Qaluobia & Assuit)

All sessions included basis & Scope of Pharmacovigilance ,how to report ADRs & interactive workshop through cases study .

On other hand ,4th wave of Pharm D candidates –Faculty of Pharmacy Cairo University completed their training by Cairo regional Center ,training included both Theoretical & practical Parts through assessment of received reports & follow up ,ending with National Database entry.







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)

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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.report@edaegypt.gov.eg
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