EGYPTIAN DRUG AUTHORITY

هيئة الدواء المصرية

The Egyptian Pharmaceutical Vigilance center

مركز اليقظة الصيدلية المصري

IN THIS ISSUE

Prepared by:

Reem Hossam

Khaled El Refaei

Designed by:

Reem Tarek

Chief editor

Aalaa Afdal

Head of Egyptian Pharmacovigilance Center

Under supervision of

Dr. Sherin Abdel Gawad

Head of the C.A for Pharmaceutical Care

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

June 2022

Volume 13 **Issue 6**

Direct Healthcare Professional Communication (DHPC): Injectable Trimebutine- Risk of Cardiac Toxicity in the Event of Misuse

EPVC in agreement with marketing authorization holders (MAH) of products containing Trimebutine would like to inform you of the following:

Summary:

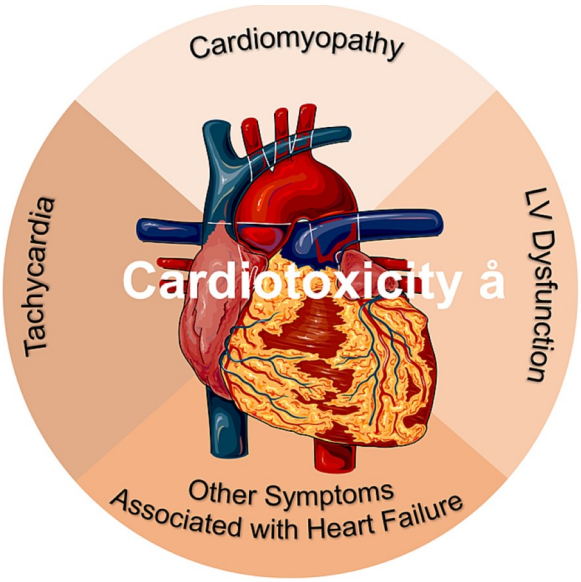
* The off-label use of trimebutine by injection is of concern with regard to its cardiac toxicity.
* A serious case of cardiorespiratory arrest has been reported in a 66-year-old patient who received multiple direct central line intravenous injections of high doses of trimebutine maleate (100 mg, 3 times daily) to treat ileus following surgery for adenocarcinoma.
* This use is no longer part of the marketing authorization indications since 2017, following a reassessment of the benefit/risk ratio (no well conducted clinical study has provided proof of the efficacy of trimebutine in paralytic ileus) .

Background:

In October 2021, a survey was carried out to assess the practices associated with the use of the injectable form of trimebutine. Thus, among the 133 health institutions located in 19 departments that responded to the survey, 99 mentioned the use of injectable trimebutine with:

⇒ non-compliance with the MA indication in approximately 48% of institutions (in particular, off-label use in postoperative paralytic ileus and use in endoscopic examinations).

⇒ non-compliance with the dosage, with high dosages (> 200 mg) in approximately 35% of institutions and very high dosages (> 400 mg) in approximately 12% of institutions.



Injectable trimebutine is reserved for the symptomatic treatment of pain, transit disorders and intestinal discomfort related to functional intestinal disorders, when the use of the oral route is not possible,

Its dosage is one intramuscular (IM) or intravenous (IV) injection of one ampoule (50 mg/5 ml) during the acute phase of intestinal disorders.

References: *ANSM (Click here)*

Case Report from Cairo: Phenobarbital - Case of Apnea

The Regional center in Cairo received a report via the E-reporting link concerning a 3 days male weighing 3.6 kg took Phenobarbital for neonatal seizure. The neonate had experienced two attacks of Apnea after administration of phenobarbital intravenously. Therefore, it was stopped and after that, Apnea recovered.

Background:

Phenobarbital Sodium [1]: Is used as

- Sedative: Sedation is obtainable within an hour, and in adequate dosage, the duration of action is more than six hours. Included in the more common conditions in which the sedative action of this class of drugs is desired are anxiety-tension states, hyperthyroidism, essential hypertension, nausea and vomiting of functional origin, motion sickness, acute labyrinthitis, pylorospasm in infants, chorea and cardiac failure. Phenobarbital is also a useful adjunct in treatment of hemorrhage from the respiratory or gastrointestinal tract. Phenobarbital controls anxiety, decreases muscular activity and lessens nervous excitability in hyperthyroid patients. However, thyrotoxic individuals occasionally react poorly to barbiturates.
- Hypnotic: for the short-term treatment of insomnia, since it appears to lose its effectiveness for sleep induction and sleep maintenance after 2 weeks
- Preanesthetic.
- Long-term anticonvulsant: (phenobarbital, mephobarbital and metharbital) for the treatment of generalized tonic-clonic and cortical focal seizures. And, in the emergency control of certain acute convulsive episodes, e.g., those associated with status epilepticus, cholera, eclampsia, cerebral hemorrhage, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics. Phenobarbital sodium may be administered intramuscularly or intravenously as an anticonvulsant for emergency use. When administered intravenously, it may require 15 or more minutes before reaching peak concentrations in the brain. Therefore, injecting phenobarbital sodium until the convulsions stop may cause the brain level to exceed that required to control the convulsions and lead to severe barbiturate-induced depression.

  Phenobarbital is indicated in pediatric patients as an anticonvulsant and as a sedative, including its preoperative and postoperative use.

Labeled information:

According to Phenobarbital Sodium Injection Summary of product Characteristics (SmPC)[1] it was stated Under section WARNINGS that:

"Too rapid administration may cause severe respiratory depression, apnea, laryngospasm, hypertension or vasodilation with fall in blood pressure. When administered intravenously, it may require 15 or more minutes before reaching peak concentrations in the brain. Therefore, injecting phenobarbital sodium until the convulsions stop may cause brain levels to exceed that required to control the convulsions and lead to severe barbiturate induced depression".

Case Report from Cairo: Phenobarbitone - Case of Apnea Continued

Recommendations for Healthcare Professionals

1. Phenobarbital Sodium Injection contains the preservative benzyl alcohol and is not recommended for use in neonates. There have been reports of fatal 'gasping syndrome' in neonates (children less than one month of age) following the administration of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse [(1)].
2. Metabolism: The plasma half-life is about 75 to 120 hours in adults but is greatly prolonged in neonates, and shorter (about 21 to 75 hours) in children. The half-life is increased in the elderly and in neonates and is prolonged by renal and hepatic disorders. There is a considerable inter-individual variation in Phenobarbital kinetics. Phenobarbital is only partly metabolised in the liver. It is about 40% plasma bound [(2)]
3. Use in Children: Phenobarbital has been reported to be associated with cognitive defects in children taking it for complicated febrile seizures. [(1)]
4. Excipient warning [(2)] : The maximum daily dose of propylene glycol should be calculated based on the product containing 0.9mg of propylene glycol per ml of undiluted product. Propylene glycol in high doses may cause central nervous system side-effects, lactic acidosis, kidney and liver toxicity, increase in plasma osmolarity, and haemolytic reactions.
5. Phenobarbital readily crosses the placenta following oral administration and is distributed throughout fetal tissue, the highest concentrations being found in the placenta, fetal liver and brain [(2)]
6. The risk of teratogenic effects developing appears to be greater if more than one antiepileptic drug is administered. The risk to the mother however is greater if phenobarbital is withheld and seizure control is lost. The risk- benefit balance, in this case, favors continued use of the drug during pregnancy at the lowest possible level to control seizures [(2)] .
7. Patients taking phenobarbital should be adequately supplemented with folic acid before conception and during pregnancy. Folic supplementation during pregnancy can help to counteract the risk of neural tube defects [(2)]

Disclaimer: The method of case handling depends on the evaluation of the treating physician according to individual patient's need.

References:

1. *Dailymed (Click here)*
2. *EMC (Click here)*

The Egyptian Pharmaceutical Vigilance center
مركز اليقظة الصيدلية المصري

Case Reports from Cairo: Acyclovir infusion - Elevated Serum Creatinine

The regional center in Cairo had received Three Cases Concerning Acyclovir drug reactions:

The First Case:
A 65-years-old male patient -weighted 95 Kg- received Acyclovir 500 mg Powder for Solution for Infusion with dose of 700 mg by IV route every 8 hrs. for Encephalitis.
On the same day, he experienced elevation in serum creatinine from 1.08 to 2.13. . The ADR stopped by stopping the suspected drug
The patient was also on valsartan 80 mg.
the patient discharged against medical advice (DAMA) the next day.

The Second Case:
A 55-years-old male patient -weighted 92 Kg- received Acyclovir 500 mg Powder for Solution for Infusion with dose of 750 mg by IV route every 8 hrs. as a treatment for suspected meningitis.
On the same day he experienced elevation in serum creatinine from 1.0 to 2.93 in one day. The drug was stopped but the serum creatinine continued to increase till it reached 4.7 on the fourth day then it started to gradually decreased till it normalized on the eighth day.
The patient was diabetic, hypertensive, and had dyslipidemia.

The Third Case:
A 59-years-old male patient -weighted 90 Kg- received Acyclovir 500 mg Powder for Solution for Infusion at a dose of 750 mg by IV route every 8 hrs. empirically for encephalitis. On the third days serum creatinine level increased from 1.0 to 2.56, upon which the suspected drug was stopped.
The serum creatinine continued to increase till 2.79 on the fourth day then the patient started to recover.
The patient was diabetic, hypertensive, and had HCV infection 2 years ago (he was treated & PCR was negative), old CVS 2 years ago.

In all 3 cases, the reaction was considered serious as it caused prolongation of hospitalization

Background:

Acyclovir: Acyclovir is an antiviral drug, in a class called synthetic nucleoside analogues and is used to treat symptoms of shingles, chickenpox, cold sores and genital herpes which are all caused by herpes viruses.

Serum creatinine test: is a way for doctors to measure how well kidneys are working. Creatinine is a waste product from the normal breakdown of muscle tissue. As your body makes it, it's filtered through your kidneys and expelled in urine.

Labeled information:

4.8 Undesirable effects
Common: Increases in blood urea and creatinine. Rapid increases in blood urea and creatinine levels are believed to be related to the peak plasma levels and the state of hydration of the patient. To avoid this effect, the drug should not be given as an intravenous bolus injection but by slow infusion over a one-hour period.
4.9 Overdose: Biotransformation:
The terminal plasma half-life in these patients was 3.8 hours. In the elderly, total body clearance falls with increasing age and is associated with decreases in creatinine clearance although there is little change in the terminal plasma half-life

Recommendations for Healthcare Professionals

1. The risk of renal impairment is increased by use with other nephrotoxic drugs. Care is required if administering i.e., acyclovir with other nephrotoxic drugs.
2. In patients receiving intravenous Acyclovir caution is required during concurrent administration with drugs which compete with acyclovir for elimination, because of the potential for increased plasma levels of one or both drugs or their metabolites(e.g. mycophenolate mofetil)
3. Care is also required (with monitoring changes in renal function) if administering Acyclovir 25 mg/ml Concentrate for solution for infusion with drugs which affect other aspects of renal physiology (e.g., cyclosporine, tacrolimus).
4. An experimental study on five male subjects indicates that concomitant therapy with acyclovir increases AUC of totally administered theophylline with approximately 50%. It is recommended to measure plasma concentrations during concomitant therapy with acyclovir.
5. Adequate hydration should be maintained. Renal impairment usually responds rapidly to the rehydration of the patient and / or dosage reduction or withdrawal of the drug.
6. The drug should not be given as an intravenous bolus injection but by **slow infusion** over a **one-hour period.**
7. In the elderly, total body clearance falls with increasing age and is associated with **decreases in creatinine clearance** although there is little change in the terminal plasma half-life, so consideration should be given to **dosage reduction** in obese patients and especially in those with renal impairment or the **elderly**.
8. The possibility of renal impairment in the elderly must be considered and dosage should be adjusted accordingly.
9. Dosage in renal impairment:

   Caution is advised when administering Acyclovir 25 mg/ml Concentrate for solution for infusion to patients with impaired renal function. Adequate hydration should be maintained.

   Dosage adjustment for patients with renal impairment is based on creatinine clearance, in units of ml/min for adults and adolescents and in units of ml/min/1.73m2 for infants and children less than 13 years of age.

References:

1. *FDA (Click here)*
2. *Pubmed (Click here)*

Pharmacovigilance Awareness Lecture in association with the Drug Information Network of the Supreme Council of University Hospitals SCUMIN

In context of the efforts regarding to the Egyptian Pharmaceutical Vigilance Center (EPVC) subordinate to the Egyptian Drug Authority to increase awareness about the concept of Pharmacovigilance and the importance of reporting adverse drug reactions of various pharmaceutical products and medical devices.

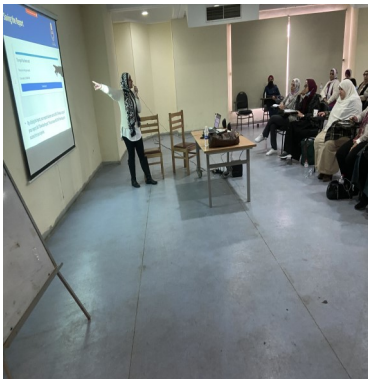
The Cairo Regional Center of pharmacovigilance, in coordination with the Supreme Council of Universities Medicines Information Network (SCUMIN), held several lectures for SCUMIN's pharmacists in several Hospitals under supervision of the Supreme Council of University Hospitals, including an introduction to pharmacovigilance and How to report Adverse Drug Reactions over three consecutive weeks (one lecture for each week).

These lectures were attended by a number of 74 pharmacists in actual attendance, in addition to attendance online via Zoom Application from various University hospitals, such as (Cairo University Hospital, Banha University Hospital, Abu Al-Rish Al-Japanese, Al-Qasr Al-Aini, etc.)

The lectures dealt with the different methods available for reporting the adverse effects of medicines and medical devices, as well as answering the various questions from the audience and the difficulties that they may encounter during reporting and how to solve them. The lecture also dealt with the critical importance of pharmacovigilance and its application in healthcare facilities, as well as the role of health care providers in hospitals in this system and discussed how to apply and practice pharmacovigilance in their facilities to assist the Egyptian Pharmaceutical Vigilance Center by taking any Regulatory Actions that may be necessary for the situation.

These lectures are part of a comprehensive plan of training across the country to spread awareness and transfer expertise on the concept of pharmacovigilance and to clarify the different methods of reporting the adverse effects of different drugs all falls within the framework of the trend towards new horizon in health care and raising the level of healthcare service in different hospitals of Egypt.





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)

The Egyptian Pharmaceutical Vigilance center
مركز اليقظة الصيدلية المصري

Address: 21 Abd El Aziz AlSoud Street. El-Manial, Cairo, Egypt, PO Box: 11451
Hotline: 15301
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

هيئة الدواء المصرية (الرعاية الصيدلية)