EGYPTIAN DRUG AUTHORITY

هيئة الدواء المصرية

IN THIS ISSUE

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EPVC
The Egyptian Pharmaceutical Vigilance center
مركز اليقظة الصيدلية المصري

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

April 2024

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Safety Notification ! Drug-induced phospholipids

The Regulatory Authority in New Zealand has published the following safety notification:

Key messages

Drug-induced phospholipidosis (DIPL) can affect any cell or organ in the body. Clinical signs and symptoms of DIPL are nonspecific. A principal histological feature of DIPL is the accumulation of phospholipids and the inducing medicine/metabolite in affected cells. Stopping the suspect medicine usually reverses intracellular changes.

What is drug-induced phospholipidosis?

Drug-induced phospholipids (DIPL) is a lysosomal storage disorder Lysosomes are cellular structures containing enzymes that break down proteins, nucleic acids, carbohydrates and lipids. A phospholipid membrane encloses the lysosome and maintains the acidic environment for the enzymes to function. In lysosomal storage disorders, undegraded material accumulates within the lysosomes of affected individuals. In DIPL, the inducing medicine causes lysosomal changes that lead to excessive but reversible accumulation of both phospholipids and the medicine in the lysosomes and the formation of lysosomal lamellar bodies. They are called lamellar bodies due to the concentric ring shape seen on electron microscopy. Given that nearly all cells contain lysosomes, and phospholipids are found in lysosome membranes, DIPL can affect any cell or organ in the body. DIPL onset may or may not be associated with clinical symptoms, including inflammatory reactions and histopathological changes, such as macrophagic infiltration or fibrosis. DIPL has been associated with organ toxicity, including of the heart, skeletal muscle, liver, lungs and kidneys.

Mechanism:

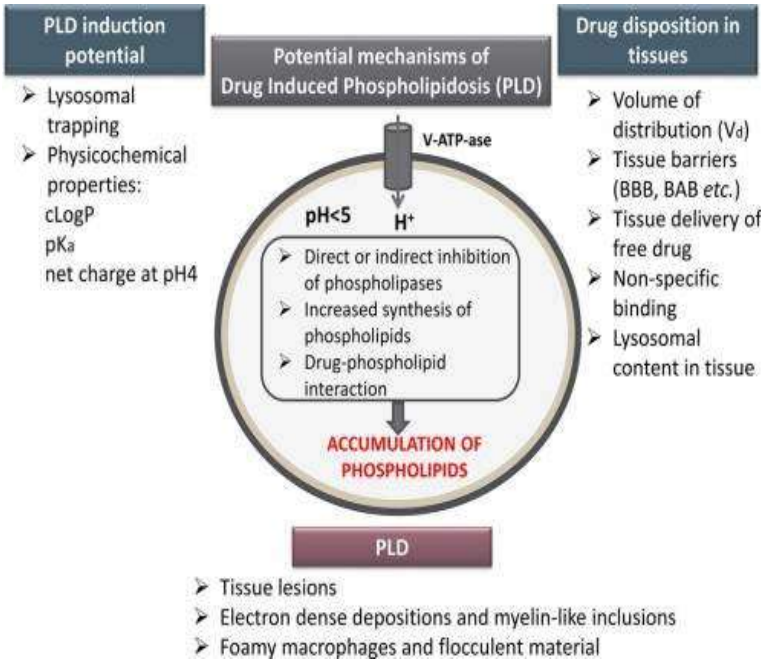
The exact mechanism of DIPL is not known, although there are two hypotheses. The first assumes that the suspect medicine binds directly to phospholipids, creating a drug-lipid complex. The complex then accumulates to form the lysosomal lamellar bodies. The second hypothesis suggests that medicines interact and inhibit phospholipase activity, resulting in an accumulation of phospholipids

Associated medicines

Over 50 medicines are associated with phospholipidosis. Examples of medicines with reports of clinically significant DIPL include:

- Amiodarone
- Fluoxetine
- Gentamicin
- Hydroxychloroquine
- Perhexiline

Treat patients presenting with signs and symptoms of organ toxicity as per local clinical guidelines. If DIPL is suspected, discontinue the suspect medicine.



Schematic illustration of potential mechanisms of drug induced phospholipidosis (PLD) in relation to drug-specific and tissue-specific characteristics. Lysosomes are the key pathophysiological targets in PLD. Vacuolar H +-adenosine triphosphatase (vATPase) is responsible for generation and maintenance of physiological pH gradient between the cytosol and lysosomes. BBB: blood–brain barrier. BAB: blood–alveolar barrier.

References:

MedSafe : *(Click Here)*

Illustrated diagram: *(Click Here)*

Safety Notification ! Fishbane Reaction: A Hypersensitivity Type to Intravenous Iron Preparations

Iron-deficiency anemia is a global health issue linked to various conditions including malabsorption, poor diet, chronic kidney disease, heart failure, cancer, and surgery. Standard therapy involves oral iron replacement, but adherence is hampered by poor taste, long-term treatment, and gastrointestinal symptoms. The IM route has been abandoned in favor of the IV route due to inconvenience with similar incidence of reported adverse events (AEs). [1].

Mechanism of Hypersensitivity Reactions (HSRs) to IV Iron Preparations

Iron reactions depend on the dosing and speed of infusion. On the other hand, it is possible that some of the reactions to iron preparations may be caused by the transient presence of labile free iron in circulation yielded from the iron–carbohydrate complex too quickly to be bound by transferrin. [1]

Risk Factors for Iron Infusion Reactions

Acute hypersensitivity reactions (HSRs) during iron infusions are very rare but can be life threatening. Major risk factors for hypersensitivity reactions include a previous reaction to an iron infusion, a fast iron infusion rate, multiple drug allergies, atopic diseases, high serum tryptase levels, asthma, and urticaria. Other risk factors are shown in the table below. [1]

History of previous infusion-related reactions to IV iron products
History of multiple drug allergies
History of severe respiratory or cardiac disease[a]
Aged >65 years[a]
History of severe asthma or eczema
Diagnosis of mastocytosis
Currently receiving a beta blocker or ACE inhibitor[a]
History of systemic inflammatory disease (eg, lupus erythematosus, rheumatoid arthritis)
History of having an anxiety disorder
[a]In the event of a hypersensitivity reaction, these risk factors are associated with worsened outcomes. ACE indicates angiotensin-converting enzyme; IV, intravenous.

Clinical Manifestation of Hypersensitivity Reactions to Intravenous Iron Preparations

According to the time latency between the administration of IV iron and the onset of symptoms, HSRs can be classified as acute when they appear during the IV iron infusion that lasts about 30 min, especially within the first 10 min, or in 1 h. after IV infusion, and less frequently, as delayed.

Immediate HSRs include anaphylaxis and isolated immediate non-life-threatening symptoms, such as local irritation, rash, urticaria, angioedema, pruritus, nausea, vomiting, diarrhea, headache and myalgia. [2]

Fishbane Reaction

Fishbane-type reactions are a specific type of transient reaction to IV iron products. Fishbane-type reactions usually consist of acute chest and back tightness and joint pain without severe symptoms, such as hypotension, wheezing, stridor, or laryngeal edema. Fishbane-type reactions occur in approximately 1 in 100 patients who receive IV iron products.

[2] Symptoms quickly recover after stopping the infusion, and they do not recur when the infusion is restarted at a slower rate. Fishbane reactions may be mistaken for prodromal symptoms of anaphylaxis [1]. The pathogenesis of Fishbane-type reactions has not been thoroughly investigated. [2]

EPVC received 13 cases of Fishbane-type reactions

Safety Notification ! Fishbane Reaction: A Hypersensitivity Type to Intravenous Iron Preparations

How are HSRs diagnosed and graded?

Reactions can be identified on the basis of subjective symptoms, objective signs and bedside monitoring. Diagnosis of an HSR does not require the presence of every feature of its category. Mild reactions can progress rapidly through moderate to severe; the latter can also occur from the outset without progression through the milder syndromes. Symptoms such as metallic taste and mild headache are part of the normal pharmacological response to IV iron and are not of clinical significance. [3] Reactions that do not fall under Fishbane-type categorization are further characterized by the severity and time to the resolution of symptoms.

The table below shows the symptoms of each category of hypersensitivity reaction, and how to properly manage each of them. [2]

Reaction subtype	Symptoms	Management
Fishbane-type reaction	Slight chest tightness	1. Stop iron infusion for ≥15 min and observe 2. Obtain vital signs (BP, pulse, respiratory rate, O_2 saturation), immediately alert supervising provider 3. Watch for symptom progression or resolution 4. Consider oxygen for hypoxia 5. Do not administer diphenhydramine 6. If unstable or symptoms worsen in 5-10 min, treat as a moderate-to-severe reaction 7. If the patient remains stable after 15 min of total observation, consider completing iron infusion at ≥50% of the previous rate 8. Observe for 1 h after infusion and document reaction
Mild hypersensitivity reaction	Transient facial flushing Headache Nausea/diarrhea Myalgia/arthralgia/lumbar pain Metallic taste Increased anxiety Itchiness Slight chest tightness	
Moderate hypersensitivity reaction	Transient cough Flushing Chest tightness Nausea Shortness of breath Urticaria Hypotension Tachycardia	1. Stop iron infusion 2. Obtain vital signs (BP, pulse, respiration rate, O_2 saturation), immediately alert supervising provider 3. Watch for symptom progression or resolution 4. Consider oxygen for hypoxia 5. Do not administer diphenhydramine 6. Consider volume load (eg, 500-mL normal saline) 7. Consider IV corticosteroid (eg, hydrocortisone) 8. If unstable or symptoms worsen, treat as a severe reaction 9. Do not rechallenge or resume current iron infusion 10. Observe for ≥1-4 h after infusion and document reaction
Severe hypersensitivity reaction or anaphylaxis	Hypotension Wheezing Stridor Periorbital edema Arrhythmia/cardiovascular collapse Unconscious or nonresponsive Respiratory arrest	1. Stop iron infusion immediately 2. Initiate immediate rapid response, Code Blue protocol 3. Do not administer diphenhydramine 4. Administer epinephrine, corticosteroids, vasopressors, Code Blue response medications as indicated 5. If unstable or symptoms worsen, transfer to intensive care unit 6. Do not rechallenge or resume current iron infusion 7. Observe for 4-24 h after infusion attempt

BP indicates blood pressure; IV, intravenous; O_2, oxygen.

PREVENTION AND TREATMENT OPTIONS

IV iron products should only be administered by trained personnel with rescue therapies available. Patients with risk factors may be considered for a cautious infusion rate.

The use of premedication's before iron infusions is lacking robust data. Notably, the following recommendations are only for patients with ≥1 risk factor or with ≥1 of the following comorbidities: asthma, inflammatory arthritis, or having more than one drug allergy. For patients with these comorbidities, premedication with a corticosteroid can be considered and should be administered 30 to 60 minutes before the initiation of an iron infusion.

Diphenhydramine is not recommended for premedication or rescue medication in Fishbane-type reactions due to adverse events, including hypotension, irritability, increased risk of falls, and anticholinergic symptoms. Its use in patients with moderate, severe, or anaphylactic hypersensitivity reactions is not recommended due to the risk of converting mild reactions into serious ones. This may lead to future complications in iron replenishment decisions. [2]

Safety Notification ! Fishbane Reaction: A Hypersensitivity Type to Intravenous Iron Preparations

Tips for Healthcare Professionals

It is important to weigh the risks versus the benefits (such as reducing the previous poor tolerance or poor absorption of oral iron) based on individual patient factor to guide treatment decisions. Allergic reactions or hypersensitivities to IV iron can arise despite having no reaction with test doses and tolerance of previous iron infusions.

It is crucial to exercise caution with every iron infusion.

Patients with at least one risk factor for infusion reactions should be considered for a cautious infusion rate of 50% of the standard rate until tolerance is shown.

For patients who tolerate an iron product at 50% of the standard administration rate should be considered as outlined by its prescribing information.

Patients with multiple risk factors for hypersensitivity reactions may be considered for dosing at 10% of the standard administration rate.

Patients with a higher risk for infusion reactions should be observed for 30 to 60 minutes after the end of the iron infusion.

Diphenhydramine is not recommended as a premedication nor as a rescue medication. [2]

Documentation of hypersensitivity reaction after resolution using a pro forma. A report of every HSR should also be submitted to the appropriate national regulatory body.

All staff involved in giving iron infusions needs regular training to ensure that when these rare events develop they are dealt with calmly and expeditiously. [3]

References:

1) ***National Library of Medicines:*** ***(Click Here)***

2) ***Journal of Hematology Oncology Pharmacy:*** ***(Click Here)***

3) ***Haematologica:*** ***(Click Here)***

Local Case Report

Safety Notification ! : Potassium chloride Contraindications

The regional center in Cairo received one case of female Child that had a cardiac arrest after the administration of Potassium chloride concurrently with Diclofenac sodium.

Drug-Drug interaction may present between Potassium chloride and Diclofenac sodium, the interaction is moderate.

Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia. Here are some precautions and /or Contraindications related to Potassium chloride use:

Potassium chloride is contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Due to the risk of developing hyperkalemia, potassium supplementation should be used with caution in patients with adrenal insufficiency (untreated Addison's disease); acute dehydration; systemic metabolic acidosis such as diabetic ketoacidosis; in patients receiving salt substitutes, potassium-sparing diuretics (e.g., amiloride, spironolactone, triamterene), ACE inhibitors, angiotensin II antagonists, cyclosporine, or tacrolimus; or in patients with renal disease, renal failure, or renal impairment. Potassium supplements should also be used cautiously in patients with severe burns because these patients are prone to hyperkalemia secondary to tissue breakdown and renal insufficiency. Serum potassium concentrations and renal function should be monitored closely in patients at risk for hyperkalemia. Because geriatric patients are more likely to have decreased renal function, potassium chloride should be dosed cautiously based on an assessment of renal function and therapeutic goals.

Additionally, depending on volume and rate of infusion, administration of potassium chloride injection can cause electrolyte imbalance, overhydration/ hypervolemia, and congested states, including pulmonary edema and peripheral edema.

Monitor patients with cardiac arrhythmias (e.g., atrial fibrillation, atrial flutter, digitalis toxicity (except due to documented hypokalemia), and ventricular arrhythmias including ventricular fibrillation and ventricular tachycardia), including patients receiving digoxin or other antiarrhythmic therapy, closely during administration of potassium chloride supplements. Patients with other cardiac disorders, such as heart failure or AV block, also require close monitoring when receiving potassium chloride.

Continuous cardiac monitoring (i.e., continuous ECG) is recommended for pediatric patients receiving higher IV doses (i.e., more than 0.5 mEq/kg/dose) and faster infusion rates (i.e., more than 0.3 mEq/kg/hour)

References:

1) What is Diclofenac ***(Click Here)***
2) What is potassium chloride:(Click Here)
3) Drug-drug interactions definition*: (Click Here)*
4) Diclofenac SPC": (Click Here)
5) Potassium chloride SPC: (Click Here)
6) Med scape drug interaction: (Click Here)
7) Drug Interactions : (Click Here)
8) Clinical Key drug monograph:
https://0810fej1m-1105-y-https-www-clinicalkey-com.mplbci.ekb.eg/#!/content/drug_monograph/6-s2.0-5067#Contraindications

Egyptian Pharmaceutical Vigilance Center (EPVC) Vigiflow expansion project Trainings for Raising Reporting Awareness

The Vigiflow expansion strategy is being continued with pleasure by the Egyptian Pharmaceutical Vigilance Center (EPVC). New cases were received through the national database, there is a noticeable increase in the organization's ICSRs so we would like to acknowledge: Alma'moura Chest, Desouq General Hospital, Kafr El-Sheikh Governorate, and Fayoum Directorate).

In addition, thanks to Secretariat of Specialized Medical Centers (SMC) organizations that enriched the national database with a huge number of reports: Qena Oncology Center, Damanhur Oncology Center, Nasser Institute, Mansours International Hospital, Elsheikh Zayed Specialized, Minya Oncology, Damietta Specialized, Albagour Hospital, Cardio Matruh. We should always be grateful for their hard work and commitment, wishing them continued success

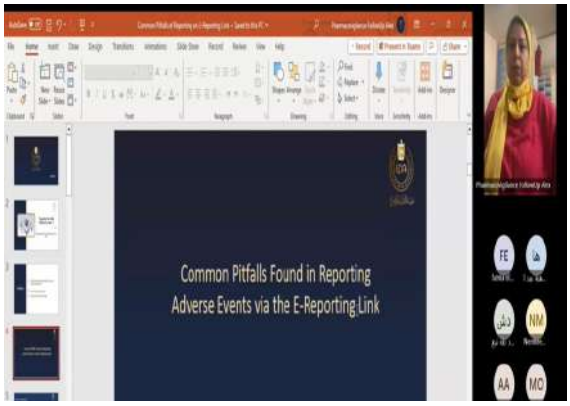
Also, we would to give special thanks to organizations with keep going of entry on our national database & those organizations named on our database (Hospitals Universities, AL Hussein University, Kas Eleiny University, Alexandria University) located under the supervision of SCUMIN "Supreme Council Of Universities Medicines Information Network", We appreciate their commitment and hope they continue to have success in their endeavors.

EPVC would like to express its appreciation to the Central Administration of Pharmaceutical Affairs, with special recognition for the outstanding cooperation of the (Giza Health Directorate, Cairo Health Directorate, Beheira Health Directorate, Al-Sharkia Health Directorate, and Damietta Health Directorate) especially with their entering of large number of reports on the national database. We are grateful for their dedication and wish them continued success in their efforts.

We are going to assess the cases that have been received and offer feedback to the coordinating organizations in an attempt to raise the caliber of the cases that have been entered into the national database.

"Together for Safe Medicine" Initiative News:

We are happy to continue the activities for the 4th wave of the EPVC initiative "Together for safe medicine". On Thursday 7 March 2024 we completed our third online lecture about Common Pitfalls found in Reporting, where we discussed with participants the common and repeated mistakes found in the ADRs reports that were uploaded on our national database vigiflow through an E-reporting link to improve the quality of received ADRs reports sent by Egyptian pharmacists that shared in 4th wave with the attendance of 150 pharmacists all over Egypt governorates, then we gave participants one more week to complete the required tasks from them concerning spreading and applying pharmacovigilance science and reporting ADRs Where after that we started our executive phase In March 2024 which will long last for 3 months of applying pharmacovigilance science and reporting ADRs through community, private and governmental pharmacies all over Egypt governorates by the help of participant pharmacists of the 4th Wave of EPVC initiative "Together for safe medicine".



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مركز اليقظة الصيدلية المصري

EPVC Tips

On Pharmacovigilance

Differences Between Addiction and Dependence

Definition of Addiction:

Addiction is the use of a substance despite negative consequences, and it can lead to physical changes in the brain affecting the reward and motivation centres, It is often accompanied by tolerance, withdrawal symptoms, and an inability to stop using the substance.

Definition of Dependence:

Physical reliance on a substance can lead to a sense of entrapment, where the body craves more and more of the drug to achieve the same effects, Dependence is characterised by tolerance and withdrawal symptoms, where the body needs more of the substance to experience the same high and experiences physical symptoms when the drug is not present.

Visit EDA website to find all medicine- related news, updates and alerts *Click here*

You will find all EPVC Newsletters and DHPCs here

You will also find all alerts regarding counterfeited and falsified products released by Central Administration of Operations *here*

The Egyptian Pharmaceutical Vigilance center
مركز اليقظة الصيدلية المصري

One report counts

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

A call for reporting

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
Hotline: 15301
Fax: +202 – 23610497
Email: 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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